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Regulatory and pro-inflammatory properties of CD4+ T-cell subsets defined by CD45RA, CCR7, CD27, and CD28 in patients with rheumatoid arthritis

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Abstract

Background/Purpose: The phenotypic classification of T cells is useful in studies of immunological diseases. Human $CD4^+$ T cells can be classified as either naive, central memory (TCM), or effector memory (TEM) cells using CCR7 and CD45RA. We recently discriminated $CD4^+$ T cells into five major subsets using four markers, CD45RA, CCR7, CD27, and CD28, and defined the function of each population based on its ability to produce IFN-γ, IL-4, and IL-2. To identify the $CD4^+$ T cell subsets most important in the pathogenesis of rheumatoid arthritis (RA), we phenotypically defined human $CD4^+$ T cells as functionally distinct subsets, and analyzed the distribution and characteristics of each subset in the peripheral blood and synovial fluid.

Methods: Peripheral blood mononuclear cells from RA patients and healthy subjects were classified into different subsets based on the expression of CD45RA, CCR7, CD27, and CD28 using five-color flow cytometry. The frequency of IFN-γ-, IL-17-, or TNF-α-producing cells, and of Foxp3- or RANKL-positive cells in each subset was analyzed by eight-color flow cytometry. $CD4^+$ T cells isolated from synovial fluid of patients with RA were also analyzed using the same method.

Results: We classified human $CD4^+$ T cells into six novel subsets based on four cell surface markers, CD45RA, CCR7, CD27, and CD28. We demonstrated that the $CD27^+CD28^+$ TCM subset comprised a significantly smaller proportion of $CD4^+$ T cells in RA patients compared to healthy controls, and within this subset, the proportion of Foxp3-positive cells was lower. In contrast, the proportion of IL-17- and TNF-α-producing cells in the $CD27^+CD28^+$ TEM subset was significantly increased in RA patients. Among the $CD4^+$ T cells from synovial fluid, only a small population of naive cells was detected, and the $CD27^+CD28^+$ TEM subset was the largest.

The percentage of cytokine-producing cells was higher in the $CD27^{-}CD28^{+}$ TCM and $CD27^{-}CD28^{+}$ TEM subsets of the synovial T cells compared with peripheral blood in RA patients.

Conclusion: These findings suggest that the total number and/or proportion of inflammatory cytokine- or Foxp3-positive cells of particular $CD4^{+}$ T cells subsets is significantly changed in RA patients. These subsets may provide novel therapeutic targets for this disease.