Novel senescent Treg subset with impaired suppressive function in Rheumatoid Arthritis

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Abstract

Objective: Premature senescence of lymphocytes is a hallmark of inflammatory rheumatic diseases such as Rheumatoid Arthritis (RA). Early T-cell aging affects conventional T-cells but is presumably not limited to this cell population; rather it might also occur in the Treg compartment. In RA, Tregs fail to halt aberrant immune reactions and disease progression. Whether this is associated with early Treg senescence leading to phenotypic and functional changes of this subset is elusive so far.

Methods: 84 RA patients and 75 healthy controls were prospectively enrolled into the study. Flow cytometry, magnetic-associated cell sorting and cell culture experiments were performed for phenotypic and functional analyses of regulatory T-cell subsets. T-cell receptor excision circle (TREC) levels and telomere lengths were determined using RT-PCR.

Results: In this paper, we describe the novel $CD4^+FoxP3^+CD28^-$ T-cell subset ($CD28^-$ Treg-like cells) in RA patients revealing features of both, Tregs and senescent T-cells: Treg surface/intracellular markers such as CD25, CTLA-4 and PD1 as well as FOXP3 were all expressed by $CD28^-$ Treg-like cells, and they yielded signs of premature senescence including reduced TREC levels and an accumulation of γH2AX. $CD28^-$ Treg-like could be generated *in vitro* by stimulation of (CD28+) Tregs with TNF-α. $CD28^-$ Treg-like cells insufficiently suppressed the proliferation of effector T-cells and yielded a pro-inflammatory cytokine profile.

Conclusion: In conclusion, we describe a novel T-cell subset with features of Tregs and senescent non-regulatory T-cells. These cells may be linked to an aberrant balance between regulatory and effector functions in RA.