A191 IMMUNE REGULATION BY PERIPHERAL TREGS INDUCED UPON HOMOTYPIC T CELL/T CELL INTERACTIONS

K Thümmler, J Leipe, A Ramming, I Prots, H S-Koops, A Skapenko *Division of Rheumatology, Med. Poliklinik, University of Munich, Munich, Germany*

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Autoimmune diseases like rheumatoid arthritis are characterised by persistently activated CD4 T cells, which circulate from the synovial tissues into the lymph nodes. Here, they encounter multiple contacts with bystander cells including resting CD4 T cells. We have recently shown that activated T cells induce the proliferation and the production of cytokines with immunoregulatory potential from resting CD4 T cells by homotypic T cell interaction. Since the compromised function of regulatory T cells results in the development of autoimmune diseases, we investigated the function of these T cells resulting from the interaction of activated T cells and resting CD4 T cells and the mechanism mediating this novel cellular interaction. Resting CD4 T cells were co-cultured with fixed activated T cells and analysed for their phenotype, cytokine secretion profile and immunoregulatory capacity.

T cells induced upon homotypic T cell interaction expressed CD25, reduced levels of CD127, transforming growth factor β, but no FOXP3. Of interest for the regulation of specific immune responses, the resulting cells strongly inhibited proliferation of CD25 negative T cells in a dose dependent manner as potently as natural occurring CD25 positive cells. Surprisingly, even polarised proinflammatory effector cells (eg, T-helper 1 (Th1) or Th17 cells) induced Tregs from memory CD4 T cells. The inhibitory effect was partly contact dependent, partly dependent on cytokines and could be abrogated by high amounts of exogenous interleukin 2 (IL-2). In vivo, Tregs resulting from the interaction of resting DO11.10 CD4 T cells and activated T cells from Balb/c mice suppressed the expansion of ovalbumin-specific T cells upon antigen challenge in the DO11.10 transfer model. Blocking adhesion receptor/counterreceptor interaction with mAbs to particular ligands revealed that the generation of regulatory T cells by homotypic T cell

contact is both, anchored and tuned through interactions between leucocyte function-associated antigen 1 (LFA-1) and its ligands, ICAM-1, -2 and -3. While blocking of LFA-1 prevented the generation of Tregs, mAbs to ICAM-1 diminished proliferation of the responder cells and neutralisation of ICAM-3 reduced IL-4 secretion.

Our data indicate a novel negative feedback mechanism via bystander immune modulation, where activated proinflammatory effector T cells induce the generation of Tregs from resting T cells. The data, thus, suggest that homotypic T cell interactions represent a physiological means to counteract sustained inflammation.

Immune regulation by peripheral Tregs induced upon homotypic T cell/T cell interactions

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