A189 IMMUNE REGULATION BY PERIPHERAL TREGS INDUCED UPON HOMOTYPIC T CELL/T CELL INTERACTIONS

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Autoimmune diseases such as rheumatoid arthritis are characterised by persistently activated CD4 T cells which circulate from the synovial tissues into the lymph nodes where they encounter multiple contacts with bystander cells including resting CD4 T cells. The authors have recently shown that activated T cells induce the proliferation and production of cytokines with immunoregulatory potential from resting CD4 T cells by homotypic T cell interaction. Since the compromised function of regulatory T cells (Tregs) results in the development of autoimmune diseases, the authors 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 naturally occurring CD25-positive cells. Surprisingly, even polarised proinflammatory effector cells (for example 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 (IL2). 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 OVA-specific T cells upon antigen challenge in the DO11.10 transfer model. Blocking adhesion receptor/counter-receptor interaction with monoclonal antibodies to particular ligands revealed that the generation of Tregs by homotypic T cell contact is both anchored and tuned through interactions between LFA-1 and its ligands ICAM-1, -2 and -3. While blocking of LFA-1 prevented the generation of Tregs, monoclonal antibodies to ICAM-1 diminished proliferation of the responder cells and neutralisation of ICAM-3 reduced IL4 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 therefore suggest that homotypic T cell interactions represent a physiological means to counteract sustained inflammation.