

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

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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.