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Regulatory T cells in human blood

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Ranjeny Thomas,[Aff1]

Aff1 University of Queensland, Australia

Keywords

Human, phenotype, regulatory T cells

Context

Three papers in the same issue of *J Exp Med* and one in *J Immunol* report the identification and characterization of human peripheral blood (PB) CD4+CD25+ regulatory T cells (see Additional information [1-4]). Subsets of CD4+ and CD8+ T cells, as well as ?d T cells and natural killer T cells, have previously been shown to have regulatory properties. Thus, these cells are broadly known as Treg (see Additional information [5]). Specifically, human and murine CD4+ T cells with regulatory function have previously been generated *in vitro* in the presence of either immature dendritic cells (DCs) or monocytes in the presence of IL-10 (called "Tr1 cells"; see Additional information [6,7]). These CD4+ cells typically secrete large amounts of IL-10, low levels of IFN? and no IL-4/5.

Significant findings

Purified CD4+CD25+ cells were predominantly of the CD45RO+ HLA-DR+ memory phenotype. Some constitutively expressed cytotoxic T lymphocyte-associated antigens-4. They expressed CD69 and CD40L upon activation, but proliferated poorly, made no IL-2, IL-4 or IFN? mRNA, and secreted little cytokine in response to mature DC. T-cell proliferation could be improved by incubation with IL-4 and IL-2. CD4+CD25+ T cells suppressed CD4+ T-cell proliferation and IFN? production in the presence of DCs, in a cell-contact-dependent manner. Either cognate interactions with antigen presenting cells (APCs), or ligation of CD3 could induce antigen-nonspecific suppression by this subset. CD4+CD25+ T cells could be expanded *in vitro* by incubation with anti-CD3 antibodies and cytokines.

Comments

The papers demonstrate that human regulatory T cells can be identified in fresh PB using the same markers as in the mouse, CD4 and CD25. The major limitation of these *in vitro* systems is the antigen nonspecificity of the suppression. *In vivo* there is evidence for 'linked' suppression of antigens co-presented by APCs, but not widespread antigen-nonspecific suppression by Treg. Thus, our understanding of the physiology has not quite reached the stage of expansion of Treg cells in vitro for autoimmune immunotherapy *in vivo*. The relationship between CD4+CD45RO+CD25+ PB T cells and the CD4+CD45RO+CD45RBdim T cells that are enriched in RA synovial fluid (SF), remains puzzling. These populations both proliferate poorly, but only the SF T populations enhance B-cell immunoglobulin production (see Additional information [8]). Do these cells belong to the same lineage, with functional differences related to their microenvironment? Would infused CD4+CD25+ T cells change function in the disease environment? Can RA SF cells suppress activated T cell responses? Revisiting SF T cell function in light of the recent findings should improve understanding of disease pathogenesis as well as therapeutic development.

Methods

flow cytometry, MLR, cytokine production

Additional information

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