

Regulatory T cells

EDITOR'S COMMENT: One of the most important papers of 2004 was that from David Hafler's group (Viglietta 2004 J.Exp.Med. 199: 971) showing that the basic immunological defect in multiple sclerosis is impaired function of a new type of cell: the "regulatory T cell". Post-doc scientist, Vicki Robertson, summarises what is known about this novel class of immune cells.

In the late 1960s and 1970s it was proposed that T cells could act as suppressor cells to suppress the immune response by producing soluble factors.¹ The existence of a dedicated population of 'suppressor' T cells was the subject of significant controversy among immunologists for many years, and by the 1980s the mechanisms behind T cell suppression had failed to be characterised by both molecular and biochemical studies. The discovery of T helper 1 (Th1) and Th2 cells led immunologists to believe that suppression was achieved through counter-regulatory cytokines and not by a distinct subset of T cells; thus the field of suppressor T cells was widely discredited. In 1993, Green and Webb even went as far as describing suppressor cells as "the nearest thing we have to a dirty word in cellular immunology".²

Over 30 years ago a series of experiments completed by Nishizuka and Sakakura³ corroborated the existence of regulatory cells (Tregs) as we know them today. These experiments demonstrated that mice thymectomised between day two and four of age developed organ specific autoimmune disease which could be prevented by 'adding back' syngeneic T cells obtained from adult thymus and spleen.³ However, until recently it has been difficult to distinguish Tregs from effector cells due to the lack of a robust expression marker.⁴ Current interest in Tregs was revived in 1995 by Sakaguchi et al⁵ who characterised the cells responsible for the prevention of organ specific autoimmunity. Sakaguchi et al showed that these regulatory cells are CD4+ T cells which express the CD25 antigen (interleukin-2 receptor α -chain), the transcription factor forkhead box P3 (FoxP3), and protect against autoimmunity in murine models of gastritis and thyroiditis.⁵

Now Tregs are regarded as separate lineages of cells with specific differentiation patterns and distinct functions, which regulate peripheral self-tolerance by suppressing the activity and expansion of autoreactive T cells. Several different subsets of Tregs have been characterised and described in the literature but they can generally be divided into two groups: Naturally occurring/innate Tregs (expressing CD4+CD25+ and FoxP3) and adaptive/inducible Tregs (Th3 and Tr1 cells) (Figure 1).

Naturally occurring Tregs

Naturally occurring Tregs are the most widely studied population of regulatory cells and constitute 8-12% of the CD4+ T cell pool in mice and 2-5% of CD4+ T cells isolated from human peripheral blood. Naturally occurring Tregs express high levels of the CD25 antigen, cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), glucocorticoid-inducible tumour necrosis factor receptor (GITR) and FoxP3.⁶ Whilst FoxP3 is currently considered the best marker for Treg identification, low expression of FoxP3 has been detected in CD4+CD25- populations and in CD8+ T cells. 'Knock in' experiments in mice have shown that FoxP3 is highly specific for Tregs and it was thought that low levels of FoxP3 detected in CD4+CD25- was likely to be due to contaminating FoxP3+ Tregs in these cell populations.⁷ However, there have been recent data to suggest that FoxP3 is expressed transiently by activated non-suppressive CD4+CD25- T cells in humans⁸ and there have been many reports of CD4+CD25+ Tregs being induced in the periphery in response to antigen from naive CD4+CD25- cells. To date no distinguishing features, either phenotypic or functional, have been found between these cells or naturally occurring Tregs.⁹

Clonal deletion of self-reactive T cells in the thymus is a major mechanism of immunologic self-tolerance, although it is uncertain how much of T cell self-reactivity can be removed by thymic negative selection, especially T cells which have T cell receptors (TCRs) for self-antigens, expressed outside the thymus.⁶ Tregs are generated in the thymus during negative selection¹⁰ and have TCRs specific for self-antigens with an intermediate affinity so that they are not deleted. Shevach et al



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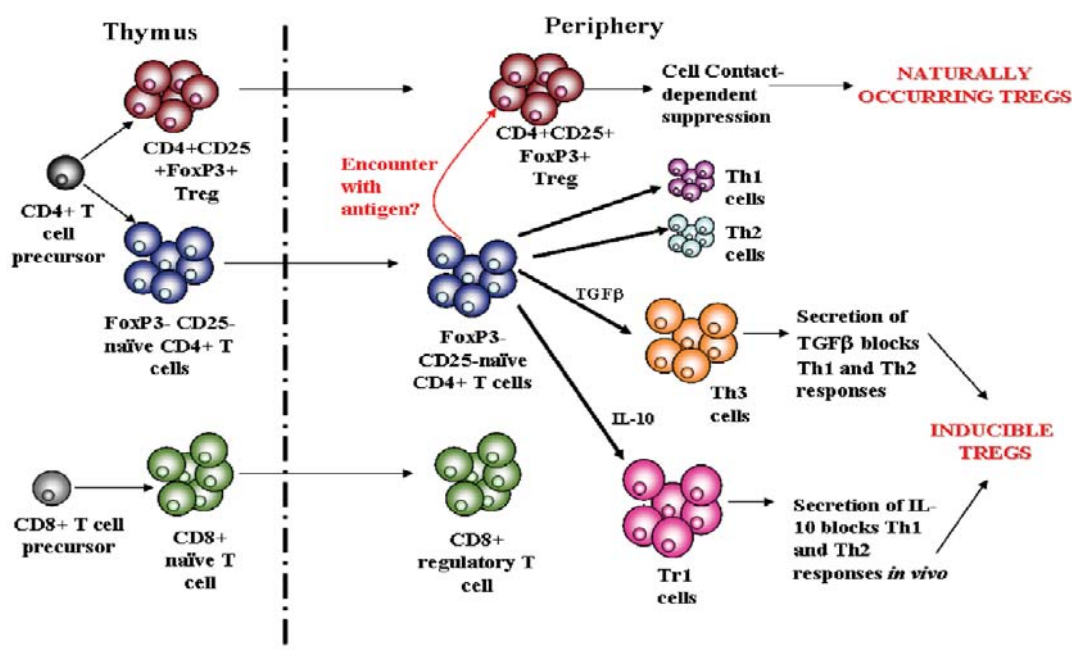


Figure 1: The development of regulatory T cells. Naturally occurring Tregs are produced in the thymus during negative selection, express CD25 and FoxP3 and mediate suppression via cell contact-dependent mechanism. CD4+CD25-FoxP3- can differentiate into Tregs in the periphery that are phenotypically and functionally identical to naturally occurring Tregs, possibly through encountering an antigen. CD4+ naive T cells can differentiate into both Th1 and Th2 cells, however if stimulated with high levels of either TGFβ or IL-10 they differentiate into Th3 or Tr1 cells respectively which exert suppression via the secretion of cytokines. CD8+ T cells can also differentiate to have a regulatory function.