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Induction of antigen specific CD4$^+$CD25$^+$Foxp3$^+$T regulatory cells from naïve natural thymic derived T regulatory cells

Bruce M. Hall *, Giang T. Tran, Catherine M. Robinson, Suzanne J. Hodgkinson

Faculty of Medicine, UNSW, Australia
Immune Tolerance Group, Faculty of Medicine, UNSW Australia, Sydney, NSW, Australia
Department of Neurology, Liverpool Health Service, Liverpool, NSW, Australia
Department of Renal Medicine, Liverpool Health Service, Liverpool, NSW, Australia

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ABSTRACT

CD4$^+$CD25$^+$FOXP3$^+$T regulatory cells (Treg) play a major role in prevention of induction and control of immune responses, and contribute to induction of immune tolerance. Natural or thymic Treg (tTreg) have non-antigen specific suppressor action. Tolerance to a specific antigen is also mediated by CD4$^+$CD25$^+$FOXP3$^+$Treg, but the source of these cells is disputed. Many suggest that they are derived from effector lineage CD4$^+$CD25$^-$FOXP3$^-$ T cells and are induced Treg (iTreg). Our work shows that tTreg with specific TCR for the antigen can be activated to more potent antigen specific Treg. We have demonstrated that initial activation of tTreg with antigen and IL-2 induces antigen specific Treg that express receptors for the late Th1 cytokines IFN-γ and IL-12. These antigen specific Treg suppress effector lineage T cells at much lower ratios than tTreg, and we call these Ts1 cells as they are activated by Th1 cytokines and express receptors for Th1 cytokines. Further activation of Ts1 cells with specific antigen and late Th1 cytokines such as IL-12 induces very potent Th1-like Treg, that express t-bet, the transcription factor for Th1 cells, as well as the Th1 cytokine IFN-γ. Similar Th1-like Treg can be induced in IL-2 activated tTreg, by IFN-γ or IL-27. tTreg activated by antigen in the presence of IL-4 induces antigen specific Treg that express the IL-5 receptor, and these Ts2 cells can be induced to Th2-like Treg by IL-5 and antigen. tTreg can be activated to antigen specific Tregs that induce tolerance and have therapeutic potential.

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1. Introduction to CD4$^+$CD25$^+$FOXP3$^+$Treg, antigen specific versus nonantigen specific

1.1. CD4$^+$CD25$^+$FOXP3$^+$Treg

CD4$^+$CD25$^+$FOXP3$^+$Treg make up the majority of peripheral CD4$^+$CD25$^+$T cells. Effector CD4$^+$ T cells on activation also express CD25, the IL-2 receptor alpha chain and can transiently express FOXP3. These activated effector T cells are a minority of peripheral CD4$^+$CD25$^+$T cells. Effector and regulatory cells lineages can be distinguished by the expression of the IL-7 receptor alpha chain (CD127), which is high on effector lineage cells and low in Treg [1].

In normal animals, the majority (70–80%) of CD4$^+$CD25$^+$T cells express FOXP3, the transcription factor that confers regulatory function on T cells. As most of these cells are derived from the thymus, they are more recently known as thymic derived Treg (tTreg), but are essentially the same populations as natural Treg (nTreg). This population of CD4$^+$CD25$^+$FOXP3$^+$Treg is not all naïve Treg and includes activated Treg and Treg induced (iTreg) from CD4$^+$CD25$^-$FOXP3$^-$T cells activated by antigen in the presence of TGF-β and absence of IL-6.

The in vivo survival of tTreg is dependent upon IL-2, and these cells are absent in IL-2 [2] and CD25 [3] as well as CTLA4 [4] knockout mice. These mice deficient in key tTreg molecules have a wide spread autoimmunity with lymphoid hyperplasia and normal immunity to antigens [5]. Effector lineage CD4$^+$T cell survival depends on IL-7 [6,7]. The homeostatic regulation of CD4$^+$CD25$^+$FOXP3$^+$Treg is controlled through IL-2 and CD25, so these cells remain at a ratio of <1:10 to effector lineage CD4$^+$CD25$^-$CD127^{high}FOXP3$^-$T cells [3].

* Corresponding author at: Room 207, Second Floor, Australian Technology Park, 4 Cornwallis St, Eveleigh, NSW 1430, Australia. Tel./fax: +61 2 92094957.
E-mail address: b.hall@unsw.edu.au (B.M. Hall).

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High concentrations of IL-2 [8], especially when combined with anti-CD3 [9] alone or with anti-CD28 [10] monoclonal antibody stimulation in vitro can cause polyclonal proliferation and expansion of $CD4^+CD25^+FOXP3^+$Treg. Such cultures are widely used to prepare tTreg for therapy in mice [11] and humans [10,12]. These in vitro expanded tTreg, suppress effector T cell activation in vitro [13] and in vivo as reviewed [14] (see Table 1). tTreg have been used as treatment in humans for GVHD [15–17] and for type 1 diabetes [18], and are planned for use in the ONE study in renal transplant recipients [19]. With the current methods of polyclonal expansion of tTreg, the numbers required to prevent rejection are extremely large and may not be achievable, unless there is massive depletion of host effector T cells, as discussed by Tang and Lee [20].

1.2. Activated antigen specific $CD4^+CD25^+FOXP3^+$Treg

The initial description of a role for $CD4^+CD25^+$T cells in immune tolerance, was the observation that animals with long surviving fully allogeneic heart grafts had $CD4^+$T cells that could transfer tolerance to irradiated host with the same donor strain heart allograft [21–23]. These tolerant cells effected rejection of third party grafts, showing alloantigen specific suppressor T cells [21–23]. These tolerant $CD4^+$T cells suppress rejection mediated by naïve $CD4^+$ and $CD8^+$T cells, as well as by memory $CD8^+$T cells, but not by memory $CD4^+$T cells [24,25]. Tolerant $CD4^+$T cells lose their capacity to transfer specific tolerance if cultured for a few days, even if stimulated by specific alloantigen [24–27]. We found lymphocyte derived cytokines in ConA supernatant could maintain the tolerance transferring $CD4^+$T cells only if stimulated by specific donor alloantigen [27]. We next examined the role of IL-2, and found depletion of $CD25^+$T cells from tolerant $CD4^+$T cells removes their capacity to transfer tolerance and left $CD4^+CD25^-$T cells that effected rejection of specific donor allografts [25,28], an observation confirmed by many others, as reviewed [29,30]. Surprisingly IL-2 alone was not sufficient to maintain full capacity of tolerant $CD4^+$T cells in culture with specific alloantigen [27], nor was IL-4 [31].

The hosts with tolerant grafts do not have increased numbers of $CD4^+$T cells or their subpopulations in blood or peripheral tissues and the ratio of $CD4^+CD25^+FOXP3^+$Treg to $CD4^+CD25^-FOXP3^-$T effector lineage cells remains <1:10. Within the $CD4^+CD25^+FOXP3^+$Treg population there [32] are the normal naïve polyclonal tTreg and antigen specific $CD4^+CD25^+FOXP3^+$Treg, so not all the $CD4^+CD25^+$T cells in tolerant host are antigen specific for the graft.

1.3. Natural tTreg that are $CD4^+CD25^+FOXP3^+$

In mice with neonatal thymectomy, the autoimmunity that develops can be prevented by transfer of $CD4^+CD25^+FOXP3^+$Treg from naïve adult animals [33] and led to the description of thymic derived T cells that prevent development of autoimmunity. These tTreg are produced in the thymus where they express IL-2Rα (CD25) and demethylate CpG in the TSDR region that leads to stable expression of FOXP3 in tTreg both in the thymus and peripheral lymphoid tissue [34,35]. The effects of these cells are nonantigen specific and they suppress all immune responses [36–39]. Full suppression of immune responses requires the $CD4^+CD25^+FOXP3^+$Treg to be at ratios of ≥1:1 with effector cells [32,38,40], summarized in Table 1. This is a non-physiological ratio, that due to homeostatic mechanism can only be transiently achieved in vivo with treatment such as an IL-2/anti-IL-2 monoclonal antibody complex [41] or by massive depletion of effector T cells and administration of tTreg.

In adoptive transfer assays, where the host has limited effector T cells, high doses of $CD4^+CD25^+FOXP3^+$Treg can suppress primary immune responses such as allograft rejection [40] or GVHD [42,43] but require ratios as high as 1:1 with effector lineages (Table 1).

These naïve polyclonal tTreg suppress by interacting with the antigen presenting cells via CTLA4, which blocks and downregulates CD80 and CD86 expression, thereby impairing activation of effector T cells by reducing activation via CD28, the second signal for T cell activation [44]. Naïve tTreg cells home to secondary lymphoid tissues, as they express CD62L [45] and CCL7 [46], and act on antigen presenting cells that have migrated to these tissues. Naïve CD62L and CD45RA [47] expressing $CD4^+CD25^+$Treg are required to suppress GVHD.

During immune responses, naïve tTreg are polyclonally expanded by IL-2 produced by activated T cells. tTreg, like effector T cells, have a repertoire of antigen specific TCR α,β expression, albeit the repertoire of TCR may be selected towards auto-antigens. Thus within naïve tTreg there are cells with specificity for immunizing antigens. The question that has interested our group is whether tTreg with TCR that recognizes antigen are activated to produce antigen specific Treg. We show that activation of tTreg with specific TCR for antigen occurs and can lead to expansion of these clones and generation of antigen specific Treg, that are $CD4^+CD25^+FOXP3^+$T cells and mainly suppress effector T cells mediating antigen specific immunity, as reviewed in [48–50] and summarized in Table 1.

Transfer of antigen specific tolerance requires large numbers of $CD4^+$T cells [22–24,28,51,52] and a high ratio of tolerant $CD4^+$T cells to naïve $CD4^+$T cells that are being suppressed [22–24,28,53]. This is probably due to that fact that there is a fine balance between Treg and effector responses. The tolerant host does not have increased proportions of $CD4^+CD25^+$Treg that remain <1:10 to $CD4^+CD25^-$T cells. Thus the existing Treg population can only suppress a small additional number of effector T cells, as there are a large number in host of $CD4^+CD25^-$T cells. When these factors are considered, tolerant antigen specific $CD4^+CD25^+$Treg are suppressing effector $CD4^+$T cells at a ratio of <1:10, as described in Table 1.

Table 1
Comparison of the ratios of Treg to effector $CD4^+$T cells used to inhibit MHC incompatible immune responses.

Treg preparation	Number given	Ratio to effector cells	Allograft model	Alloantigen specific	Reference
Tolerant $CD4^+$T cells	2×10^7	4:1	Cardiac	Yes	[24,25,28]
(<10% $CD4^+CD25^+$T cells)*	($1–2 \times 10^6$)	(1:10–1:20)			
Naïve $CD4^+CD25^+FOXP3^+$T cells	5×10^6	1:1	Cardiac	No	[40]
Naïve $CD4^+CD25^+FOXP3^+$T cells		1:1	GVHD	No	[42,43,55,213,214]
Naïve tTreg cultured with alloantigen and IL-2		4:1	Skin	Yes?	[215]
Naïve tTreg cultured with alloantigen and IL-2		2:1	GVHD	No?	[57,213]
Naïve Treg cultured with Alloantigen, IL-2 &TGF-β		1:2	GVHD	?	[213]
Treg from anti-CD4 mAb DST mice		5:1	Cardiac	Yes	[141,216]
Treg from anti-CD4 mAb DST mice		5:1	Skin	?	[141,216,217]
Treg induced from naïve $CD4^+$T cells by alloantigen & IFN-γ		4:1	Vascular graft	Yes	[125]
Treg induced from naïve $CD4^+$T cells by alloantigen & IFN-γ		5–2:1	Skin graft	?	[123]
Ts1 induced from naïve tTreg by IL-2 & alloantigen		1:10	Cardiac	Yes	[84]
Ts2 induced from naïve tTreg by IL-4 & alloantigen		1:10	Cardiac	Yes	[84]
Th1-like Treg from Ts1 cells cultured with IL-12 & alloantigen		1:100	Cardiac	Yes	[104]

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