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The Regulatory T Cell Family: Distinct Subsets and their Interrelations

Helmut Jonuleit and Edgar Schmitt

The immune system, a highly effective and dynamic cellular network, protects a host from pathogens. Therefore, the immune system must distinguish self from nonself structures, but also between harmful and innocuous foreign Ags to prevent nonessential and self-destructive immune responses. The induction of Ag-specific T cell tolerance and its maintenance in the periphery are critical to prevent autoimmune immune responses. A still growing body of evidence reveals that specific T cell populations that have suppressive/regulatory properties tightly control autoimmune immune responses. Among the CD4+ regulatory T cells (Tregs)1 basically two different subsets of Tregs can be differentiated by their distinct suppressive mechanisms. Naturally occurring CD4+CD25+ Tregs exert their suppressive effects obviously via cell contact by membrane-bound molecules although the nature of these molecules is still elusive. The suppressive capacity of the second subset, Th3 and type 1 T regulatory (Tr1) cells, is contact independent and is based mainly on cytokines such as IL-10 and TGF-β. It seems that these cells, in contrast to naturally occurring CD4+CD25+ Tregs, represent altered states of differentiation rather than a unique cell lineage. However, the interrelationship of these distinct subsets of CD4+ Tregs is currently a matter of debate.

Naturally occurring CD4+CD25+ Tregs

The idea of a naturally occurring T cell subset with suppressive function that limits the outcome of autoimmune responses was first described in the 1970s by Gershon (1). However, at that time neither the cells nor the hypothetical soluble suppressor factors responsible for the observed effects were characterized, and several inconsistencies discredited the whole concept for a long period of time. This conception was revived by studies showing that a subset of peripheral CD4+ T cells, which coexpress the IL-2R α-chain (CD25), is critical for the control of autoreactive T cells in vivo (2). Mice, thymectomized before day 3 after birth, lack this population of resident CD4+CD25+ cells, resulting in the development of various autoimmune diseases (3). Furthermore, depletion of CD25+ T cells in adult mice results also in the development of various autoimmune diseases, such as gastritis and thyroiditis (2). Subsequent in vitro studies showed that this population, now referred to as CD4+CD25+ T regulatory cells, is both anergic and suppressive (4–6).

CD4+CD25+ Tregs were originally identified in mice. However, more recently, a comparable population of T cells with identical phenotypic and functional properties has been defined in rats and humans (7–11). They represent 5–10% of all peripheral CD4+ T cells. Freshly isolated CD4+CD25+ Tregs are hyporesponsive to allogeneic or polyclonal activation in vitro (12). However, they suppress the proliferation of conventional CD25− T cells in coculture and suppression occurs only when the CD4+CD25+ Tregs are activated through their TCR (13). Once activated, the inhibitory capacity of CD4+CD25+ Tregs is Ag nonspecific, that means suppression is independent of the Ag specificity of the responding T cell population (4). However, the inhibitory activity in vitro is strictly dependent on cell contact to CD25− T cells and independent of soluble suppressive cytokines (7, 12). The exact mechanism by which CD4+CD25+ Tregs exert their suppressive effects remains unknown. However, the ultimate result of this suppression is the inhibition of IL-2 transcription in the responder cell population (4). The suppressive effect and the hyporesponsive state of CD4+CD25+ Tregs can be overcome by exogenous IL-2 and IL-15 (4, 7, 9).

CD4+CD25+ Tregs are characterized by the constitutive expression of several activation markers including glucocorticoid-induced TNFR (GITR) family-related protein (14), OX40 (CD134) (15), L-selectin (CD62L) (16), and CTLA-4 (CD152) (17). The significance of these molecules with respect to the suppressive properties of CD4+CD25+ Tregs is currently controversial. Blocking mAb against OX40 or L-selectin showed no effect on suppressive activity of CD4+CD25+ Tregs in vitro. In contrast, Takahashi et al. (18) have shown in the murine system that anti-CTLA-4 mAb reverses the suppressive function of CD4+CD25+ Tregs in vitro, whereas Chai et al. (19) could not find any inhibitory effect of anti-CTLA-4 mAb. Additionally, it was postulated that membrane-bound TGF-β might be responsible for the inhibitory activity of murine CD4+CD25+ Tregs (20) and Annunziato et al. (21) observed that the suppressive capacity of human CD4+CD25+ thymocytes can be blocked by a combination of mAb against CTLA-4 and membrane-bound TGF-β in vitro. However,

1 Abbreviations used in this paper: Treg, regulatory T cell; GITR, glucocorticoid-induced TNFR; Tr1, type 1 T regulatory; MBP, myelin basic protein; DC, dendritic cell.

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these results have been difficult to reproduce by others (4) and anti-CTLA-4 mAb or blocking Fab against CTLA-4 or against TGF-β showed no effects on the suppressive activity of peripheral human CD4⁺CD25⁻ Tregs (7, 9, 22). Furthermore, membrane-bound TGF-β is down-regulated on human CD4⁺CD25⁺ Tregs and up-regulated on conventional CD4⁺CD25⁻ T cells after activation (23). Finally, CD4⁺CD25⁺ Tregs with full suppressive activity can be isolated from TGF-β-deficient mice and in agreement with this, wild-type CD4⁺CD25⁺ Tregs suppress conventional CD25⁻ T cells that cannot respond to TGF-β because they express a dominant-negative TGF-β receptor (24). Therefore, the potential role of TGF-β and CTLA-4 in the suppressive mechanisms remains controversial. A major point of criticism regarding the above-mentioned studies is certainly that both, membrane-bound TGF-β and CTLA-4 are also expressed on activated conventional CD4⁺CD25⁻ T cells. Thus, in case a biological effect was observed, one could not differentiate whether this effect was a result of the binding of blocking Abs to CD25⁺CD4⁺ Tregs or to conventional CD4⁺ T cells.

GITR, a member of the TNFR family, is another marker predominantly expressed on CD4⁺CD25⁺ Tregs in the thymus and periphery (14). Stimulation through a GITR-specific mAb abrogated the suppressive activity of freshly isolated murine CD4⁺CD25⁺ Tregs in vitro and treatment with the same mAb in vivo induced an autoimmune gastritis, whereas other organ-specific autoimmune diseases could not be observed (14). Binding of GITR expressed by preactivated CD4⁺CD25⁺ Tregs cannot inhibit the suppressive properties of these cells and activated conventional CD4⁺ T cells, which also express GITR, exert no suppressive activity, thus showing that GITR is not suppressive per se (15). These data imply that engagement of GITR possibly prevents the induction of suppressor activity in resting CD4⁺CD25⁺ Tregs but is not involved in the cell contact-dependent suppressive mechanism itself. In agreement with this assumption is the observation that human T cells do not express GITR ligands (25), thus excluding a direct participation of GITR in the Treg-target cell interaction. In conclusion, CD25, OX40, L-selectin, CTLA-4, and GITR are useful markers for phenotypic identification of naturally occurring CD4⁺CD25⁺ Tregs in a nonactivated immune system but might not be critically or at least exclusively involved in contact-dependent suppression.

Regarding the development and function of CD4⁺CD25⁺ Tregs, the transcription factor FoxP3 was recently found to play a key role (26–28). Originally, it was described that mice expressing a naturally occurring loss-of-function mutation of FoxP3 (scurfy mice) rapidly develop a fatal lymphoproliferative disease similar to that seen in mice lacking CTLA-4 or TGF-β (29). Detailed analyses revealed, that CD4⁺CD25⁺ T cells from scurfy mice lack suppressive activity, indicating that they do not represent Tregs. Scurfy mice could be rescued by transferring wild-type CD4⁺CD25⁺ T cells and it was also shown, that FoxP3 is directly involved in the development of Tregs (28). FoxP3 is exclusively expressed in murine CD4⁺CD25⁺ Tregs and ectopic expression of FoxP3 in conventional CD4⁺CD25⁻ T cells conferred suppressor function to this T cell subset (26, 28). These data clearly indicate that FoxP3 is critical for both development and function of Tregs in mice, and these finding separate FoxP3 from other Treg-associated markers such as CD25 and GITR, which are expressed more generally on activated T cells (30).

Finally, CD4⁺CD25⁺ Tregs were isolated from murine peripheral lymphoid organs but it has been demonstrated that CD25⁺CD4⁺ thymocytes also have strong suppressive properties as evidenced in vitro and by adoptive transfer studies (31). Furthermore, the human counterpart of these Tregs has been isolated and characterized from pediatric thymus (10). Hence, CD4⁺CD25⁺ Tregs most possibly develop in the thymus like conventional CD4⁺ T cells. This assumption was further substantiated by the finding that murine CD25⁺CD4⁺ thymocytes strongly express the Treg-specific transcription factor FoxP3, which has been shown to be essentially involved in the development of CD4⁺CD25⁺ Tregs and the acquisition of their suppressive properties (26–28). Consequently, the obvious ability of the thymus to generate CD4⁺CD25⁺ Tregs and conventional CD4⁺ T cells simultaneously raised the question, which mechanisms are responsible for the selection of CD4⁺CD25⁺ Tregs vs conventional CD4⁺ T cells? Several approaches using thymus-specific expression of an Ag in combination with T cells expressing a transgenic TCR recognizing this Ag revealed that CD4⁺CD25⁺ Tregs are positively selected on MHC class II-positive cortical epithelium cells in case their receptor receives a signal with intermediate strength from MHC-antigenic peptide complexes (32, 33). Thus, the selection process in the thymus leads to three different results depending on the affinity of the TCR: 1) low affinity leads to positive selection of conventional CD4⁺ T cells, 2) intermediate affinity leads to positive selection of CD4⁺CD25⁺ Tregs, and 3) high affinity leads to depletion of the thymocytes (34). Therefore, these results from the transgenic models suggest that CD4⁺CD25⁺ Tregs are positively selected in wild-type mice after recognizing self-peptides in association with MHC class II with intermediate affinity (Fig. 1).

**Induced CD4⁺ Tregs**

Another class of CD4⁺ Tregs has been described whose suppressive properties are, in contrast to naturally occurring
CD4+CD25+ Tregs, cell contact independent and mediated mainly through soluble suppressive cytokines such as IL-10 and TGF-β (Table I). These cells are secondary suppressor T cells and develop from conventional CD4+CD25− T cells in the periphery. It seems that these cells represent altered states of differentiation rather than a unique T cell lineage. Two types of secondary T regulatory cells have been described as Tr1 (35) and Th3 cells (36). Tr1 cells are defined by their ability to produce large amounts of IL-10 and low to moderate levels of TGF-β, whereas Th3 cells produce preferentially TGF-β.

The generation of Tr1 cells from naive or resting CD4+ T cells in vitro was first described by Groux et al. (37). They showed that naive T cells from OVA-TCR-transgenic mice were repeatedly stimulated with OVA and IL-10, differentiated into T cells with a unique cytokine profile distinct from Th1 or Th2 cells. These Tr1 cells produce IL-10, some IL-5, and IFN-γ, with or without TGF-β, but showed only marginal or no IL-2 and IL-4 production. Meanwhile, such Tregs have been characterized in humans and, more recently, it has been shown that IL-10-producing Tregs can also be induced by stimulation of resting human CD4+ T cells with a combination of anti-CD3 and anti-CD46 Abs (38). Tr1 cells proliferate poorly after polyclonal or Ag-specific activation in vitro and functional studies on Tr1 cells revealed that these cells have immunosuppressive properties and can prevent the development of T cell-mediated autoimmune responses (39). Tr1 can control the activation of naive and memory T cells both in vitro and in vivo and suppress Th1- and Th2-mediated immune responses to pathogens, tumors, and alloantigens (40). Furthermore, supernatants of activated Tr1 cells strongly reduce the capacity of dendritic cells (DC) to induce alloantigen-specific T cell proliferation (39, 41). The suppressive effects of Tr1 cells are reversed by blocking Abs against IL-10, showing that the inhibitory capacity of Tr1 cells is mainly mediated through production of immunosuppressive IL-10 (37, 39).

Th3 cells were originally identified in mice after oral tolerance induction to myelin basic protein (MBP) (42). After treatment with MBP, the majority of MBP-specific CD4+ T cells secrete TGF-β and suppress the induction of a MBP-specific experimental autoimmune encephalitis in vivo (43). This suppression was abrogated by injection of anti-TGF-β Abs. Furthermore, these Th3 cells suppress the proliferation and cytokine release of MBP-specific Th1 cells in vitro in a TGF-β-dependent manner (42). Therefore, regulatory Th3 cells are a unique T cell subset induced by orally administered Ag in vivo and triggered in an Ag-specific fashion. They provide help for IgA production and have suppressive properties for Th1 and Th2 cells (36). However, the suppressive effects of Th3 cells are Ag nonspecific and mediated as bystander suppression through secretion of TGF-β. Because TGF-β is broadly expressed and influences the functional activity of multiple cell types, TGF-β-secreting Th3 cells probably have a major role in many aspects of immune regulation and T cell homeostasis (44).

Although there is little evidence for cytokine-mediated differentiation of naturally occurring CD4+CD25+ Tregs, TGF-β and IL-10 are important for generation of Tr1 and Th3 cells (35, 36). IL-10 acts as a differentiation factor for murine Tr1 cells and it has been also demonstrated that human CD4+ T cells differentiate in the presence of IL-10 and IFN-α into Tr1 cells (35, 45). Furthermore, supernatants of activated human Tr1 cells promote the differentiation of naive CD4+ T cells into Th1 cells in an IL-10-dependent manner (35). Alternatively, a combination of the immunosuppressive drugs vitamin D3 and dexamethasone has also been shown to induce the development of Tr1 cells in vitro from naive human or murine CD4+ T cells (46). Finally, addition of TGF-β to cultures of murine T cell precursors promotes the induction of Th3 cells, and expansion of Th3 cells can be further enhanced by the presence of IL-4 and IL-10 (36).

Regulatory Tr1 and Th3 cells arise from naive or resting CD4+ T cells in the periphery and a large body of literature suggests that the type and activation state of DC as professional APC control the differentiation of naive T cells into Tregs (47). For instance, it has been shown that murine pulmonary DC induce the development of IL-10-producing Tregs. This ability depends on inducible costimulator-inducible costimulator ligand interactions leading to IL-10 production by the pulmonary DC themselves (48). Induction of DC maturation by inflammatory stimuli is the key process in directing naive T cells to differentiate into effector T cells (Th1 or Th2). In contrast, in the steady state, immature DC are rather tolerogenic and favor the development of Tregs, possibly as a strategy for the maintenance of immunological tolerance (47, 49). Several protocols have been developed to enhance the tolerogenic potential of DC and irreversibly convert the functional properties of DC (50, 51). Such functionally blocked DC can no longer respond to inflammatory stimuli and induce Tregs that suppress a broad range of effector T cell responses. Key cytokines for modulation of DC differentiation are IL-10 and TGF-β. This finding opens the possibility for a relationship of DC and regulatory Tr1/Th3 cells. Activated Tr1 and Th3 cells suppress the T cell stimulatory properties of DC and might induce tolerogenic DC that then promote the differentiation of naive CD4+ T cells into Tr1 cells.

Table I. Characteristics of naturally occurring and induced CD4+ T regulatory cells

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>CD4+CD25+ Tregs</th>
<th>Tr1</th>
<th>Th3</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD25</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>2, 13, 35, 36</td>
</tr>
<tr>
<td>GITR</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>14, 15</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>4, 13, 16–23, 36</td>
</tr>
<tr>
<td>FoxP3</td>
<td>+</td>
<td>−</td>
<td>?</td>
<td>26–30</td>
</tr>
<tr>
<td>Cytokine secretion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-10</td>
<td>+/-</td>
<td>+++</td>
<td>+</td>
<td>7, 9, 13, 39</td>
</tr>
<tr>
<td>TGF-β</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>13, 35, 36, 39</td>
</tr>
<tr>
<td>Differentiation factors</td>
<td></td>
<td>IL-10, IFN-α,</td>
<td>TGF-β, IL-4</td>
<td>36, 39, 40, 44</td>
</tr>
<tr>
<td>Suppressive mechanism</td>
<td></td>
<td>Cell contact</td>
<td>IL-10, TGF-β</td>
<td>TGF-β</td>
</tr>
<tr>
<td>In vivo</td>
<td>Cell contact, IL-10, TGF-β</td>
<td>IL-10, TGF-β</td>
<td>TGF-β</td>
<td>52–56</td>
</tr>
</tbody>
</table>
Most investigators have found that the suppressive properties of CD4+CD25+ Tregs in vitro are strictly cell contact dependent and independent of soluble agents (13). Nevertheless, the suppressive properties of Tregs in vivo are obviously even more complex and based on diverse mechanisms including mediators like IL-10 and TGF-β that are important for systemic suppressive effects (52, 53). For example, control of autoimmune responses in a murine inflammatory bowel disease model by CD4+CD25+ Tregs depends on IL-10 and TGF-β (44) and CD4+CD25+ Tregs from IL-10-deficient mice fail to protect immunodeficient mice from a T cell-mediated wasting disease (54). Otherwise, IL-10-deficient CD4+CD25+ Tregs retain full suppressive activity in vitro (4). Additionally, TGF-β was found to be essential for suppression of colitis by CD4+CD25+ Tregs in mice (55), but CD4+CD25+ Tregs from TGF-β1 knockout mice also retain their suppressive activity in vitro (24). Collectively, these findings strongly suggest that in vivo CD4+CD25+ Tregs and TGF-β/IL-10-producing cells, most possibly Tr1 and Th3 cells, intimately cooperate to prevent autoimmune reactions. Moreover, it is conceivable that CD4+CD25+ Tregs directly induce the development of other Treg subsets. Several lines of evidence, paraphrased by the terms “bystander suppression” and “infectious tolerance,” indicate that in mice suppressive properties are transferred from Tregs to conventional CD4+ T cells (56). In agreement with this hypothesis, it was shown recently that human CD4+CD25+ Tregs in vitro do not only suppress their target cells but also convey suppressive properties to the cocultured conventional CD4+ T cells, thereby inducing Th suppressor cells (23, 57). This secondary suppressive activity, transferred from CD25+ Tregs via cell-cell contact, is itself cell contact independent and mediated by the well-known immunomodulatory factors TGF-β (23) and IL-10 (57) and was circumscribed with the term infectious tolerance. Thus, controversial data on the role of cytokines for the suppressive mechanism of CD4+CD25+ Tregs in vivo might be explained by the transfer of tolerizing activity from naturally occurring CD4+CD25+ Tregs to induced T regulatory cells with a different Ag specificity. This spreading of suppression from naturally occurring Tregs to conventional CD4+ T cells might be one of the fundamental mechanisms for induction and maintenance of peripheral tolerance.

We have shown that human CD4+CD25+ Tregs induce Th suppressor cells that produce TGF-β (23) after activation, whereas others published that CD4+CD25+ Tregs induce IL-10-producing Th suppressor cells (57). This inconsistency can be reconciled by the very recent finding showing that human blood contains two distinct subsets of CD4+CD25+ Tregs that induce secondary suppressor T cells with different phenotypes (our unpublished data). Human CD4+CD25− Tregs can be distinguished due to the expression of distinct integrins. CD4+CD25− Tregs expressing the αβ-integrin convert energized CD4+ T cells into IL-10-producing Tr1-like cells, whereas αβ-integrin Tregs induce TGF-β-producing Th3-like cells. Additionally, both subsets of human naturally occurring Tregs express FoxP3 and induce the expression of this transscription factor in cocultured CD25+ CD4+ T cells.

The integrins αβ and αβ are homing receptors for cellular migration of T lymphocytes to inflamed tissues and to mucosal sites, respectively (58). The αβ-integrin binds to VCAM-1, which is induced on the endothelium of inflamed tissues, whereas the αβ-integrin binds to vascular adrenergins, selectively expressed by venules in mucosal tissues (58). Therefore, it can be postulated that the distinct subsets of human CD4+CD25+ Tregs are specialized to migrate in vivo to distinct tissues where they counteract autoreactive T cells in a cell contact-dependent manner and possibly also promote the differentiation of suppressed T cells into Th3 or Tr1 cells which then are responsible for systemic suppression via IL-10 and TGF-β (Fig. 1).

There is clear evidence that functionally distinct subsets of CD4+CD25+ Tregs with different phenotypes also exist in mice. Lehmann et al. (59) first described unique subsets of murine CD4+CD25+ Tregs identified by presence or absence of the integrin αβ− (CD103) and showed that Tregs expressing CD103 have in particular the capacity to prevent inflammatory bowel diseases. Therefore, the authors postulated that CD103−expressing Tregs might be specialized for cross-talk with epithelial environments. In addition, Banz et al. (60) have demonstrated that CD103+CD4+CD25+ Tregs are enriched in gut-associated tissue and control wasting disease and T cell homeostasis, whereas the CD103−CD4+CD25+ Tregs could not control autoimmune reaction in this model. Both subsets, CD103− and CD103+, Tregs suppress in vitro conventional CD4+ T cells in a contact-dependent manner. In addition, the CD103− subset does not only suppress the target cells but also induces IL-10 secretion by cocultured CD25+ CD4+ T cells.

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