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Brief Reviews

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CD4$^+$FOXP3$^+$ T Regulatory Cells in Human Autoimmunity: More Than a Numbers Game

S. Alice Long and Jane H. Buckner

Regulatory T cells (Treg) play a dominant role in suppression of autoimmune pathology, as rescue of Treg number and/or function in model systems can both prevent and reverse disease. These findings have generated a series of studies addressing the role of defects in Treg number and function in human autoimmunity. However, demonstrating global defects in Treg of individuals diagnosed with autoimmune diseases has been challenging. These challenges are founded, in part, in the complexity of human autoimmune diseases in which various genetic factors and environmental triggers contribute to disease susceptibility. Moreover, contribution of failed Treg-mediated suppression to pathogenesis can extend to multiple mechanisms. In this article, we discuss what is known with respect to the number and function of CD4$^+$FOXP3$^+$ Treg in human autoimmunity, focusing on representative autoimmunediseases in which there are diverse Treg-mediated defects. We also highlight the need to better understand Treg plasticity and function in the context of autoimmunity. *The Journal of Immunology*, **2011, 187: 2061–2066.**

In the mouse, a lack of CD4$^+$FOXP3$^+$ regulatory T cells (Treg) results in increased autoimmunity, and adoptive transfer of Treg prevents and reverses autoimmunity (1). In humans, a lack of functional Treg also leads to autoimmunity, as is seen in individuals who have immunodysregulation polyendocrinopathy enteropathy X-linked syndrome due to mutations in *FOXP3*. These individuals develop aggressive autoimmunity, including insulin-dependent diabetes, thyroiditis, and eczema (2, 3). An extension of these observations is the premise that defects in Treg number or function contribute to the development of human autoimmune disorders. However, identifying overt defects in Treg-mediated immune regulation in the common human autoimmune diseases has been difficult. This may be due to the heterogeneous nature of human autoimmunity and the fact that both genetic and environmental factors contribute to disease. Moreover, there are significant differences in the expression of FOXP3 between mice and humans that may impact direct translation of mouse studies to the clinical setting. In this brief review, we focus on what is known with respect to CD4$^+$FOXP3$^+$ Treg in selected human autoimmune diseases for which compelling data exist regarding the role of Treg in disease. These selected autoimmune diseases include the organ-specific diseases type 1 diabetes (T1D) and multiple sclerosis (MS); a prototypic systemic autoimmune disease, systemic lupus erythematosis (SLE); and rheumatoid arthritis (RA), an autoimmune disease for which Treg found at the site of autoimmune attack (synovial joint) have been examined.

Identification and location of human Treg

An obvious first step in determining whether deficits in Treg contribute to human autoimmune disease is to assess whether there are decreased numbers of Treg, thereby leading to impaired regulation. Initially, Treg were defined by high expression of CD25, the high-affinity IL-2R (4–6), and more recently, by intracellular staining for FOXP3 (7). Based on these criteria, multiple studies assessed the frequency of CD4$^+$CD25^{high} and FOXP3$^+$ T cells in PBMC of subjects diagnosed with T1D, MS, and RA, and found no differences in the frequency of these cells in comparison with controls (8–16). Yet, isolated reports showed changes in the frequency of FOXP3$^+$ T cells in these diseases. In MS, both an increase (17) and decrease (18) in FOXP3$^+$ Treg were observed, and in RA and new-onset T1D an increase in FOXP3$^+$ Treg was found (19, 20). In contrast, decreased frequencies of CD25^{high} and FOXP3$^+$ T cells were consistently observed in SLE subjects (reviewed in Ref. 21) and, in fact, decreased CD4$^+$CD25^{high} T cell frequencies often correlated with disease severity (22–26). This observation was extended to the tissues, demonstrating that this decrease represents a global reduction in Treg, not preferential accumulation of Treg in lymph nodes or the diseased kidney (25). Taking CD25^{high} and FOXP3 studies together, it appears that SLE is either unique in its decrease in Treg number, or alternatively, that the systemic nature of the disease may allow detection of differences in Treg number in peripheral blood.

Treg number in the periphery may be normal in some organ-specific diseases, yet Treg at the site of disease pathology may be inadequate, a hypothesis supported by studies in the NOD mouse model of diabetes (27). To address this possibility, one can measure the relative number of Treg to effector T cells

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Abbreviations used in this article: aTreg, adaptive regulatory T cell; MS, multiple sclerosis; nTreg, natural regulatory T cell; RA, rheumatoid arthritis; SLE, systemic lupus erythematosis; T1D, type 1 diabetes; Teff, effector T cell; Treg, regulatory T cell.

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(Teff) within the affected organ. Studies of cells from the synovial joints of RA patients and cerebral spinal fluid of MS subjects have consistently shown increased FOXP3$^+$ cells relative to total CD4 T cells (9, 13, 28). This increase in FOXP3$^+$ cells in the tissues affected by autoimmunity raises several questions. 1) Are FOXP3$^+$ cells functional Treg or recently activated Teff that transiently upregulate FOXP3? 2) What is the appropriate number of Treg in the setting of inflammation? 3) If the numbers are adequate, is there a failure of Treg function at these sites? In answer to the first question, we now know that FOXP3 is expressed at high levels in Treg, but also, in activated Teff, although transiently and at lower levels (29), making FOXP3 an imperfect marker of Treg in humans, particularly in the setting of inflammation. Recently, new markers have been identified that allow the distinction between nTreg from other FOXP3-expressing T cells. These include measures of methylation of the FOXP3 locus and expression of the transcription factor helios (30). These markers, as well as those that distinguish functional subsets of Treg (see below), will assist in clarifying the question of whether Treg numbers are inadequate in disease. The question of what number of Treg is appropriate in the setting of inflammation has been nicely studied in the context of inflammatory bowel disease where FOXP3$^+$ T cells are increased in the gut (31, 32). In these studies, the inflammatory condition due to infection, diverticulitis, was compared with the autoimmune inflammation of Crohn's disease, and a similar ratio of Treg to effector CD4 T cells was found in both inflammatory conditions. This suggests that, at least in the gut, the number of Treg at the site of disease is adequate and supports the possibility that defects in Treg-mediated function are present.

Beyond FOXP3

Quantification of Treg is predicated on possession of a unique and consistent phenotype. However, FOXP3$^+$ T cells are not a uniform population, but instead, consist of phenotypically and functionally diverse populations, some of which have been shown to be pliable, especially in the setting of inflammation. In humans, the majority of studies of Treg performed to date have used either CD25 or FOXP3 as markers of Treg. Yet, there is a growing appreciation for the diversity and plasticity of human Treg, which has implications with respect to peripheral Treg subset function, generation, stability, and persistence (33–35). These findings are likely to be germane to human autoimmunity and are discussed below.

Multiple types of FOXP3$^+$ T cells

It is now well accepted that there are two major types of CD4$^+$ FOXP3$^+$ Treg known to suppress immune responses: natural Treg (nTreg) and adaptive Treg (aTreg). nTreg are a stable subset derived from the thymus and are thought to control reactivity toward self Ags. aTreg are derived from CD25$^-$ T cells in the periphery, are less stable, and are thought to regulate responses upon antigenic exposure in the periphery (34, 36). Cells recently exiting the thymus, including nTreg, can be identified in the periphery by CD31 and CD45RA expression. In MS, a decrease was found in the proportion of CD45RA$^+$CD31$^+$ FOXP3$^+$ Treg (37), a population known to have potent suppressive capacity (38, 39). Segregation of FOXP3$^+$ T cells into resting CD45RA$^+$FOXP3^{low} Treg, activated CD45RA$^-$FOXP3^{high} Treg, and CD45RA$^-$FOXP3^{low} T cells delineates resting and FOXP3^{high} activated Treg with suppressive function from nonsuppressive CD45RA$^-$ FOXP3^{low} T cells capable of secreting cytokines (39). Using CD45RA expression to differentiate FOXP3$^+$ cells, differences in FOXP3$^+$ subsets in SLE (39) and recent onset T1D children (20), but not T1D adults (40), were found. In this same adult T1D cohort, demethylation of the FOXP3 T cell-specific demethylation region locus, a characteristic of nTreg (41), did not differ from controls (40). Together, these data suggest that alterations in the composition of Treg are present in autoimmune diseases. These changes may be transient and related to the stage of disease and, in part, may be due to impaired Treg subset generation and/or stability.

Through altered signals from either intrinsic or extrinsic factors, inadequate induction of FOXP3$^+$ aTreg may also play a role in autoimmune diseases. The relative contribution of nTreg and aTreg in influencing autoimmune susceptibility and pathogenesis is not well understood. Mouse models strongly suggest a dominant role for nTreg, yet aTreg clearly play a key role in limiting tumor clearance (42) and function in that setting of a tissue-restricted self Ag (43). Deciphering unique phenotypes and functional attributes of nTreg and aTreg is essential to better understand the relative contribution of each Treg subset in human autoimmune disease. Multiple factors contribute to the generation of aTreg, which requires both IL-2 and TGF-β (44). Neither polyclonal nor islet Ag-specific generation of aTreg was impaired in T1D subjects (45, 46). However, IL-2 failed to increase aTreg generation in T1D subjects (40). As defects in IL-2 and TGF-β are associated with SLE (47, 48), one would expect to observe impaired Treg generation, consistent with the low number of Treg found in the periphery of SLE subjects. Altered costimulation, including TLR engagement, and the inflammatory microenvironment may also impinge on Treg induction and function (49–51). Studies to better understand the impact of these factors in human autoimmunity are currently underway.

TCR signal strength and proliferative capacity of Treg clearly play a role in Treg biology. However, a disconnect exists between in vitro assays of isolated Treg and in vivo analyses. Isolated Treg are relatively anergic in vitro, requiring strong TCR stimulation to divide. In contrast, it has been clearly demonstrated in mouse models that Treg proliferate in vivo and attenuated TCR signal strength impacts thymic selection and nTreg generation (52). Whereas addressing proliferation in humans is more difficult due to limitations in decisive phenotypic markers of Treg and access to labeling techniques, some elegant in vivo experiments have been performed. Using deuterium labeling, both CD45RA and CD45RO Treg were shown to proliferate in vivo, with the CD45RO subset being a rapidly dividing population (53). Using a similar technique, studies are currently underway to determine the proliferative capacity of Treg in human autoimmune disease. Although defects in TCR signaling are clearly involved in human autoimmunity and human self-reactive T cells express low-avidity TCR (54), direct assessment of the impact of altered TCR signal strength on Treg generation in humans is yet to be measured. Together, these data suggest that multiple factors influence Treg biology that may not be reflected in in

vitro cultures. A greater understanding of in vivo Treg characteristics and development of more precise isolation and in vitro assays is required to understand the role of TCR signal strength and proliferation of Treg in human autoimmune disease.

Recently, there is a greater appreciation for the lack of stability and survival of Treg subsets of both mice and humans. Persistence of FOXP3 expression in $CD25^{high}$ T cells was shown to be diminished in T1D subjects, in part, due to decreased response to IL-2 (40). Similarly, maintenance of FOXP3 expression is impaired in SLE (55); however, this was due to enhanced TNF stimulation. Another measure of Treg instability is coexpression of FOXP3 and inflammatory cytokines (i.e., IFN-γ) (33, 56). In T1D children, increased IL-17–secreting $FOXP3^{low}$ T cells were observed as compared with age-matched controls (20), further supporting the observation that Treg in T1D subjects may be less stable. Treg are often characterized as being prone to apoptosis (57). Treg of SLE and T1D, but not MS subjects displayed increased susceptibility to apoptosis (25, 58, 59). Overall, these defects in stability and survival may result in inadequate numbers or function of Treg in sites of inflammation.

Differential expression of surface receptors, in addition to CD25, discriminates between functionally distinct $FOXP3^+$ T cell subsets in control subjects. Low expression of CD127 on $CD4^+CD25^{high}$ cells can more precisely identify stable $FOXP3^+$ Treg in control subjects (60, 61). In MS subjects, an increase in the frequency of CD127-expressing cells within the $FOXP3^+$ population correlated with poor Treg function (18, 62), but no difference in the frequency of $CD25^{high}$ $CD127^{low}$ Treg was found in peripheral blood of T1D subjects (63, 64). The ectonucleotidase, CD39, is highly expressed on some $CD4^+FOXP3^+$ Treg and confers function through hydrolysis of ATP (65). These $CD39^+FOXP3^+$ Treg were decreased in PBMC of MS subjects as compared with controls (66, 67), but have not been evaluated in other diseases. Although further studies are certainly warranted, early data suggest that deficiencies in unique Treg subsets may be involved in different human autoimmune diseases.

Treg-mediated function in human autoimmunity

Failure of Treg function may be due to a lack of Treg with the specificity required to suppress inflammation in an organ, cell-intrinsic defects, or extrinsic factors that impede Treg function. Measurement of Treg function is most often assessed in vitro through coculture of Treg and effector T cells. In these in vitro assays, competent Treg suppress cytokine production and proliferation of target cells. When comparing Treg isolated from autoimmune patients and controls, most consistently, a decrease is observed in Treg-mediated function of T1D (8, 12, 15, 46, 68) and MS (11, 16, 62, 69, 70) subjects. Whereas a number of studies report defects in Treg-mediated suppression in SLE subjects (71–73), others do not (25, 26). When reduced Treg-mediated function was observed, it did not correlate with disease activity (74). In contrast, defects in Treg-mediated suppression of proliferation have not been observed in RA subjects (9, 13). Thus, impaired in vitro Treg-mediated function is observed in T1D and MS, but more variably in SLE and RA, suggesting heterogeneity in the role of functional Treg-mediated defects. However, several key caveats must be considered when interpreting these data. Differences in the function of Treg across autoimmune diseases may be due to variation in the composition of the Treg compartment. To isolate viable cells for in vitro analysis, a high enough frequency of Treg that share unique surface markers must be used. Most studies rely on $CD25^{high}$ expression, with more recent studies incorporating additional phenotypic markers (i.e., CD127, CD45R). Moreover, as discussed above, in vitro culture of Treg may fail to reflect in vivo biology.

Source of impaired Treg-mediated suppression in autoimmunity

Defects in suppression may occur due to Treg-intrinsic defects, resistant effector cells, or proinflammatory properties of APC (Fig. 1). A handful of studies addresses the source of defective Treg-mediated suppression. To determine whether defects in suppression arise from Treg-intrinsic defects, Treg from patients can be cocultured with target cells from control subjects. Using this experimental design, two studies found that Treg from the majority of T1D subjects were capable of suppressing target cells of control subjects (46, 64). However, in another study, a decrease in IL-10 production was observed in cocultures of Treg and Teff of T1D subjects (12), suggesting that IL-10 production by T1D Treg is impaired. Defective suppression was reversed in MS (16, 37, 62) and SLE (75) when Treg of control subjects were used in cross-cultures, strongly suggesting that Treg are the major source of impaired suppression in these subjects. Functional defects in Treg-mediated suppression in RA subjects were generally not observed (71, 76, 77); however, when suppression of cytokines by RA Treg was measured (76), a selective loss of suppression of IFN-γ secretion was seen without diminished proliferation. This selective suppression was associated with overexpression of TNF-α in the synovial tissues of RA subjects, decreased FOXP3 expression, and impaired CTLA-4 expression (77).

More recently, the impact of APC and Teff resistance on $FOXP3^+$ Treg-mediated suppression has been explored in the

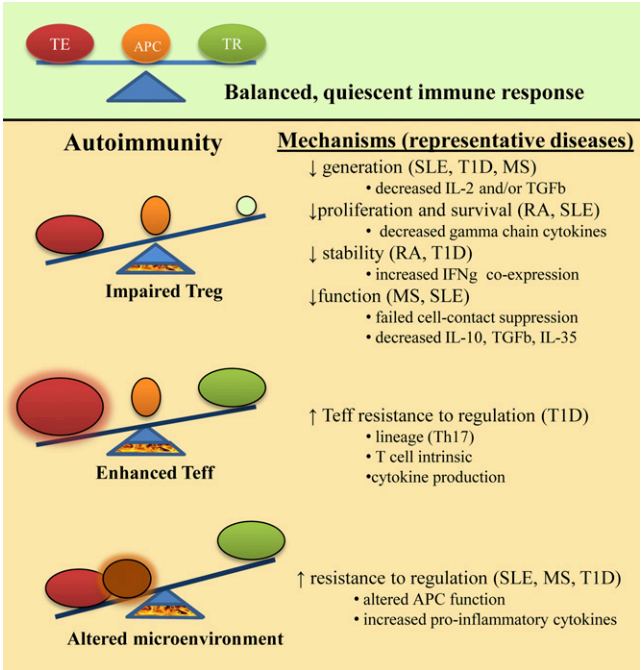

FIGURE 1. Multiple mechanisms control loss of tolerance in autoimmunity and reflect the heterogeneity of autoimmunity between individuals and diseases.

setting of human autoimmunity. Multiple factors can contribute to Teff resistance to Treg (78, 79). These include the developmental stage and lineage of the T cell (80); exposure to the common γ-chain cytokines IL-2, IL-7, IL-15, and IL-21 (81); and expression of the TNFR family OX40Ls (82) and 4-1BB (83). Resistance of Teff to Treg-mediated suppression has been shown in T1D (46, 64) and SLE (74), but not to date in RA or MS. In T1D this was observed even when anti-CD3/anti-CD28 beads were used as artificial APC, thereby demonstrating that the Teff was the source of defective Treg-mediated suppression (46). APC facilitate resistance to Treg-mediated suppression through varied mechanisms, including altered differentiation and metabolic properties and increased proinflammatory cytokine production (84, 85). In SLE, impaired Treg-mediated suppression was only observed when autologous APC were present, strongly suggesting a dominant role for the APC in these subjects (72, 75). Thus, impaired function may be present due to intrinsic defects in Treg, as seen in MS; effector cell resistance, as is most evident in T1D; or proinflammatory properties of APC, as observed in SLE. Regardless of the source of impaired Treg-mediated regulation, it is important to determine whether these defects are causative and/or are secondary to autoimmune pathology.

Implications from genetic associations

HLA is clearly the genetic association most strongly linked to autoimmunity (86), and its impact with respect to Treg is most likely on the repertoire and specificity of the $CD4^+$ $FOXP3^+$ Treg selected in the thymus. In the past decade, a number of large genome-wide association studies have revealed polymorphisms in genes that are associated with autoimmunity. Whereas genome-wide association studies have lesser relative risk than HLA, the preponderance of variants in immune cells and commonality between selected autoimmune diseases suggests dysregulation of specific immunological processes in related autoimmune diseases (87, 88). As it may relate to Treg biology, variants in three genes in the IL-2R signaling pathway (*IL-2*, *CD25*, and *PTPN2*) are associated with T1D, and also MS, SLE, and RA, with varying degree and specificity (89–91). Variation in soluble serum IL-2RA has been shown to correlate with variants in *CD25* (92, 93) and may contribute to impaired Treg-mediated tolerance, as soluble IL-2RA can limit Treg response to IL-2 (94) and decreased response to IL-2 correlates with an autoimmune-associated *PTPN2* variant (95). Impaired response to IL-2 correlates with diminished FOXP3 expression in T1D subjects (40). Multiple autoimmune-associated genetic variants result in altered TCR signal transduction, including PTPN22 1858T, which leads to blunting of the TCR signal (96, 97) and may contribute to failed selection of nTreg or functional defects in peripheral Treg (98). RA-associated variants of *FCRL3* have been correlated with impaired Treg function (99, 100). Common polymorphisms and rare variants in negative costimulatory molecules expressed on Treg, including PD-1 and CTLA-4, are associated with multiple autoimmune diseases (88), but the impact of these autoimmune-associated polymorphisms on Treg biology has not been definitively demonstrated. Most likely, the global disease-associated impact of these susceptibility alleles is conferred through the combined biological effects on multiple cell types. However, the genetics of autoimmunity does implicate pathways that impact Treg biology, and this information may be used to discover mechanisms by which Treg-mediated dysfunction occurs.

Therapeutic interventions and Treg

Certainly, drugs can modulate Treg biology in both intended and unexpected ways, leading to challenges in understating the global mechanistic effect of therapeutics. Some of the therapies currently used to treat autoimmune diseases include treatments that clearly induce changes in $CD4^+FOXP3^+$ Treg number and function. Whether these act directly on Treg or indirectly by altering the inflammatory milieu or pathogenic cells is not always clear. Corticosteroid treatment of SLE (101, 102) and IFN-β and glutamire acetate treatment of MS (18, 101, 103) have been correlated with increased frequencies of Treg. However, treatment of MS with daclizumab (blocking CD25 Ab) resulted in decreased Treg numbers, yet this decrease in Treg number did not correlate with clinical responses (104). Treatment of RA with infliximab (blocking TNFR Ab) was associated with increased Treg numbers that correlated with an improved clinical outcome (76). Certainly, as our knowledge of Treg biology increases and our ability to accurately and reproducibly measure Treg number and function in the context of chronic inflammation and therapy improve, tracking Treg may become a useful measure of efficacy for some treatments of autoimmune diseases. This knowledge will also guide development of therapies designed to enhance the stability and function of Treg by increasing Treg number and/or altering the milieu in which Treg act in vivo. Such studies, including adoptive Treg therapy, are currently underway and will help us directly determine whether Treg deficits in autoimmunity can be rescued by simply augmenting Treg numbers.

Conclusions

Although studying Treg in human autoimmune diseases has been difficult and at times findings have been contradictory, the bulk of the data suggests that defects in Treg-mediated suppression are present in human autoimmunity. Defects in the regulation mediated by Treg appear to differ from disease to disease and occur through multiple mechanisms within a disease cohort. For example, greater defects in Treg number are observed in SLE, whereas decreased Treg function is observed more readily in MS and Teff resistance is more prevalent in T1D. Importantly, this diversity extends beyond each disease to the level of the individual reflecting the clinical heterogeneity of each autoimmune disease. Ongoing research in both basic immunology and translational studies of human immune-mediated diseases promises an enhanced understanding of Treg biology, including gaining a better understanding and appreciation for the diversity of Treg subsets, plasticity of these cells, and Treg function in the context of chronic autoimmune inflammation and therapy. Ultimately, definition of the specific defects in Treg-mediated regulation that participate in human autoimmune diseases in each individual may lead to improved diagnosis, treatment, and cure of disease through data-driven, individualized medicine.

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