Regulatory T Cell Therapy for Autoimmune Disease

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It has now been well documented in a variety of models that T regulatory T cells (Treg cells) play a pivotal role in the maintenance of self-tolerance, T cell homeostasis, tumor, allergy, autoimmunity, allograft transplantation and control of microbial infection. Recently, Treg cell are isolated and can be expanded *in vitro* and *in vivo*, and their role is the subject of intensive investigation, particularly on the possible Treg cell therapy for various immune-mediated diseases. A growing body of evidence has demonstrated that Treg cells can prevent or even cure a wide range of diseases, including tumor, allergic and autoimmune diseases, transplant rejection, graft-versus-host disease. Currently, a large body of data in the literature has been emerging and provided evidence that clear understanding of Treg cell work will present definite opportunities for successful Treg cell immunotherapy for the treatment of a broad spectrum of diseases. In this Review, I briefly discuss the biology of Treg cells, and summarize efforts to exploit Treg cell therapy for autoimmune diseases. This article also explores recent observations on pharmaceutical agents that abrogate or enhance the function of Treg cells for manipulation of Treg cells for therapeutic purpose.
[Immune Network 2008;8(4):107-123]

INTRODUCTION

The concept of immunosuppression was initially proposed by Gershon *et al* in the early 1970s when they demonstrated that tolerance to sheep red blood cells, induced upon the injection of high doses of the tolerogen, was not only a T-cell-dependent phenomenon but that it could be transferred to naïve hosts upon the infusion of T cells from the tolerant mice (1). The term "infectious tolerance" was coined to describe the phenomenon (2) and the term "suppressor cells" was coined to describe a subset with suppressive activity (1). It has been considered to be one of the most important discoveries in immunology in this century made by Gershon and his student Kondo. Ha *et al* obtained more direct evidence for the presence and migration of suppressor cells. Thymocytes collected 24 hr after a large intraperitoneal dose of bovine gamma globulin (BGG), washed, and transferred to normal hosts produced a specific deficit in the recipients of both humoral and cell-mediated response to BGG. This effect was mediated by cells of low to intermediated density and was inhibited by treating these cells before transfer with antimycin A or cycloheximide, but not mitomycin C or actionomycin D. Thus the transferred tolerance depended on an active process involving living specific regulatory cells and protein synthesis. And the term "thymic suppressor cells" was named to describe thymocytes with suppressor activity (3-5). Evidence was accumulating to support the concept of thymic regulatory or suppressor function in a number of other experimental systems (6-10).

However, since the hypothetical soluble suppressor factor could not be identified on a molecular level and since appropriate cellular markers were lacking at that time, the suppressor T cells concept and even the existence of suppressor T cells was drawn into question for a considerable time (11,12). Despite these adverse circumstances, numerous experiments were performed that gave clear indication that such cells may indeed exist (6,9,10,13-21). The whole concept of suppression and suppressor T cells was revived by a few papers published in the mid-1990s. In 1995, Sakaguchi *et al* were first discovered CD4+CD25+ regulatory T cells (22). They demonstrated that transfer of lymphoid-cell populations from which CD4+ T cells expressing the α-chain of the IL-2 receptor (IL-2Rα; also known as CD25) into athymic BALB/c nude mice had been removed caused spontaneous development of various T cell-mediated autoimmune diseases. Furthermore, reconstitution with CD4+CD25+ T cells pre-

Received on September 4, 2008. Revised on September 19, 2008. Accepted on September 24, 2008.
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Keywords: autoimmune diseases, rapamycin, regulatory T cells, superantigen, suppressor T cells

vented the development of autoimmunity. CD4+CD25+ T cells were named regulatory T cells (Treg cells) and since then have been intensively characterized by many groups (23-28). Now the terms "suppressor T cells" and "regulatory T cells" are sometime used interchangeably, but the term "Treg cells" is preferred by most researchers. It has been now been well documented in a variety of models that CD4+CD25+ Treg cells play indispensable roles in the maintenance of natural tolerance, in averting autoimmune responses, as well as in controlling inflammatory reactions. Anyhow, this great discovery challenged traditional theories about clonal deletion being the only mechanism of self-tolerance and provided convincing evidence that self-antigen-reactive T cells that cause autoimmune disease can be controlled through active suppression by natural Treg cells.

BIOLOGY OF REGULATORY T CELLS

CD4+CD25+ Treg cells, which constitute 5 10% of peripheral T cells in mice, are continuously produced in thymus as a functionally mature T-cell population that includes cells with immunosuppressive activity *in vitro* and *in vivo*. However, CD25 is not a definite definitive marker of natural Treg cells, namely CD25 is an activation marker for T cells and is therefore also expressed by effector Th1 and Th2 cells (28,29). Many subsets of Treg cells have been identified, including CD4 CD25 Treg cells, Tr1 cells, Th3 cells, CD8 T cells, γ δ-TCR cells, NK T cells, and NK⁻ α β-TCR CD4⁻ CD8⁻ double negative (DN) Treg cells (30-35). It is now firmly established that there are two major categories of Treg cells described to date (Fig. 1). The first is the naturally occurring, thymically derived CD4+CD25+ Treg cells (nTreg cells) that express high level of the transcription factor Foxp3, which is essential for their development and function (36-38). The other category is the antigen-specific Treg cells (iTreg cells), which can be induced *in vitro* and *in vivo* under particular conditions of antigenic stimulation. These antigen-specific Treg cells secrete anti-inflammatory cytokines such as IL-10 and/or TGF-β, and regulate immune responses and inflammatory pathologies (39). iTreg cells that secrete IL-10 are often referred to as IL-10-Treg cells, or Tr1 cells and those that secrete TGF-β have been referred to as Th3 cells. However, many questions remain to be answered regarding distinct roles of these Treg cell subsets during immune response. In addition, recently, both murine and human DN Tregs have been shown to suppress allogeneic immune responses in an Ag-specific fashion (40). DN Tregs have been demonstrated to enhance donor skin, islet, and heart graft survival and play a role in preventing graft-vs-host disease (41,42). DN Treg-mediated suppression requires cell-cell contact and occurs via direct cytotoxicity toward T cells (40). However, much remains unknown regarding the mechanisms

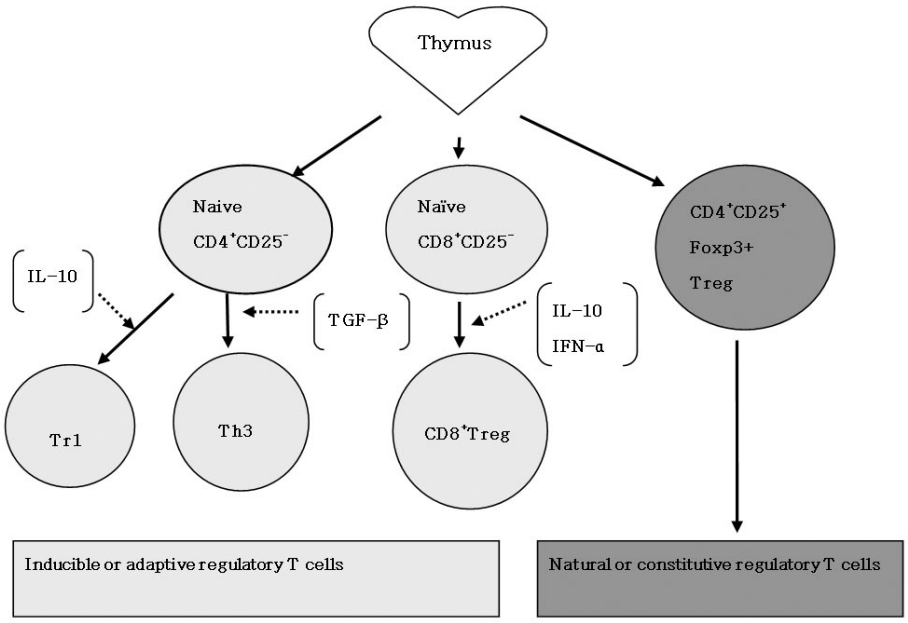

Figure 1. Natural and inducible regulatory T cells. Natural T cells (nTreg) express the cell-surface marker CD25 and transcription factor forkehad box p3 (Foxp3). These cells mature and migrate from the thymus. Other populations can be induced from naïve T cells in the periphery in response to antigen stimulation under the influence of IL_10, TGF-beta and possibly IFN-gamma. There are both natural (or constitutive) and inducible (or adaptive) populations of regulatory T cells (Treg). Tr1, Type 1 regulatory T cells; Th3, T helper 3 cells.

whereby DN Tregs can interact with and kill Ag-specific syngeneic CD8 T cells. These observations led attempt to find alternative markers of regulatory T cells. Thus, identifying discriminatory cell-surface marker for the characterization and isolation of Treg cells has always been a crucial goal. The isolation and therapeutic manipulation of Treg cells requires the use of reliable surface receptors that are selectively up-regulate in Treg cells. Although there are excellent markers for mouse Treg cells, this goal has remained elusive for human Treg cells. Traditionally, mouse and human Treg cells have been characterized as CD4+CD25. However, the purity of isolated human Treg cells has always been an issue because T cells upregulate CD25 expression upon activation. Indeed, during the influenza or allergy season, a substantial proportion of human CD4+ T cells can express CD25 (29,43). Putative surface molecules for regulatory T cells include cell-surface expression of lymphoid homing receptors CD38, CD621, CD103 (integrin $\alpha_E\beta_7$), cytotoxic T-lymphocytes antigen-4(CTLA-4), glucocorticoid induced tumor necrosis factor receptor related protein (GITR), the chemokine receptors CCR4 and CCR8, low levels of cell-surface CD45RB expression, lymphocyte activation gene-3 (LAG-3), intracellulaur expression of the transcriptional repressor forkhead box P3 (FOXP3) (44). FOXP3 seems to be the most promising key marker of natural regulatory T cells and was reported to be essential for the development and functional activity of CD25+ Treg cells (36,37). In addition, Foxp3 gene transfer was shown to convert naïve CD4+CD25- T cells into a functional regulatory population, demonstrating the pivotal role of Foxp3 in Treg cell biology (23,36,37). Importantly, although the identification of FOXP3 as a key regulator of Treg-cell development and function has facilitated their identification in mice, many activated (non-regulatory) human T cells also express FOXP3, precluding it as a useful marker for human Treg cells. Namely, expression of FOXP3 mRNA is not confined to CD4+CD25+ T regulatory cells in humans (29,43). Consequently, the search for Treg-cell specific cell-surface markers, particularly in humans, has continued in earnest with a growing number of candidates proposed (45-47). Interestingly, it was recently demonstrated that Treg cells expressed a higher level of folate receptor 4 compared with activated effector T cells (48) and Treg cells express latency-associate peptide (LAP) on their surface. These CD4+CD25+LAP+ cells express elevated levels of Foxp3 and Treg associated molecules (CTLA-4, GITR gene). In a model of experimental allergic encephalomyelitis (EAE), CD4+CD25+LAP+ cells exhibit more potent suppressive acivity than CD4+CD25+LAP- cells, indicating that LAP is an authentic marker able to identify a TGFβ-expressing CD4+CD25+Treg subpopulations (49). Furthermore, Bruder *et al* have shown that neuropilin-1 (Nrp1) that is a multifunctional protein, identified principally as a receptor for the class 3 semaphorins and members of the vascular endothelial growth factor (VEGF) family is constitutively expressed on the surface of CD4+CD25+ Treg cells independently of their activation state (50). More interestingly, Battagglia *et al* have observed that in human lymph nodes, Nrp1 identified a small regulatory CD4+CD^{high} T-cell subpopulation (Nrp1+Treg) that expressed higher levels of FOXP3 message and protein than Nrp1- Treg and various molecular markers of activated Treg, i.e. CD45RO, HLA-DR and GITR and that Nrp1 Treg cells were more efficient than Nrp1$^-$ Treg cells at inducing suppression. In addition, they showed that Treg cells and Nrp1+ Treg cells levels dropped in the tumor-draining lymph nodes of patients with cervical cancer following preoperative chemoradiotherapy in a direct relationship with the reduction of tumor mass, suggesting that suppressor cell elimination facilitated the generation of T cells mediating the destruction of the neoplastic cells left behind after cytotoxic therapy. It is also interesting that Nrp1 is a receptor for transforming growth factor β-1 and promotes regulatory T cell activity (51). Despite the mechanistic complexity, Treg cells are potent suppressors and they play a pivotal role in the control of autoimmunity, allergy, and transplantation tolerance (13,16,52).

This review attempts to outline current understanding of immunobiology of Treg cells and provides an update on the role of Treg cells in cell-based intervention autoimmune diseases. In addition, I discuss new findings in relation to possible targeting of Treg cell for immune modulation of the diseases and focuses on the potential therapeutic application of Treg cells in this exciting field. In this Review, unless otherwise stated, I primarily focus on thymus-derived, naturally occurring D4+CD25+Foxp3+/FOXP3+ T cells.

REGULATORY T CELL THERAPY FOR AUTOIMMUNE DISEASES

It is not surprising that Treg cells play an important role in the control of autoimmunity. This role is exemplified best by experiments involving reconstitution of immunodeficient nude mice with CD4+ T cells that were depleted of CD25+ cells. CD4+ CD25- T subset reconstituted nude mice develop

various organ-specific autoimmune diseases, such as gastritis, oophoritis. orchitis and thyroiditis as shown in Fig. 2 (22,53-55).

Infusion of the CD4+CD25+ subset in nude mice prevents the onset of these diseases (Fig. 3). The protective value of CD4+CD25+ cells against organ-specific autoimmunity has also been shown in several other models of autoimmunity (53). Male mice that carry the *scurfy* mutation, null mutation of the Foxp3 gene ($Fox3^{sf}$), lack Treg cells and exhibit severe lymphoproliferation and infiltration of multiple organs by inflammatory cells, particularly the skin and liver (37,53). The requirement for FOXP3-controlled Treg cells is also true in human, since patients with IPEX (the immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome), who lack FOXP3, exhibit very severe autoimmune pathologies (36,53,56). It is becoming increasingly clear as shown in Fig. 4 that Treg cells impinges on the development of a variety of autoimmune diseases, including rheumatic arthritis (57-74), type 1 diabetes (75-84), glomerulonephritis (85-90), experimental allergic encephaomyelitis (91-99), multiple sclerosis (100-106), systemic lupus erythematosus (107-115) , inflammatory bowl diseases (116-122), autoimmune gastritis (123,124), myasthenia gravis (125-128), autoimmune thyroiditis (129-131), and acquired aplastic anemia (132,133).

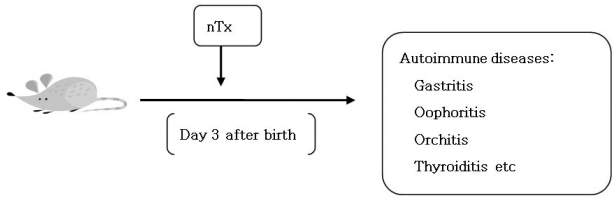

Figure 2. Induction of autoimmune disease in mice by manipulating thymus. Neonatal thymectomy (nTx) 3 days after birth leads to the development of autoimmune diseases such as gastritis, oophoritis, orchitis, thyroiditis, prostatitis, sialadentitis (See text for details).

Rheumatic arthritis (RA)

Accumulating evidence suggests that RA is a T-cell-mediated autoimmune disease and Treg cell defects in RA (126,134). The role of CD4+CD25+ T cells in pathogenesis and regulation of arthritis has been best studied in a mouse model of RA, collagen-induced arthritis (CIA). Depletion of Treg cells with anti-CD25 antibody before the onset of arthritis has been shown to result in increased cellular and humoral immune responses and increased arthritis severity (58) and adoptive transfer of CD4+CD25+ T cells was shown to result

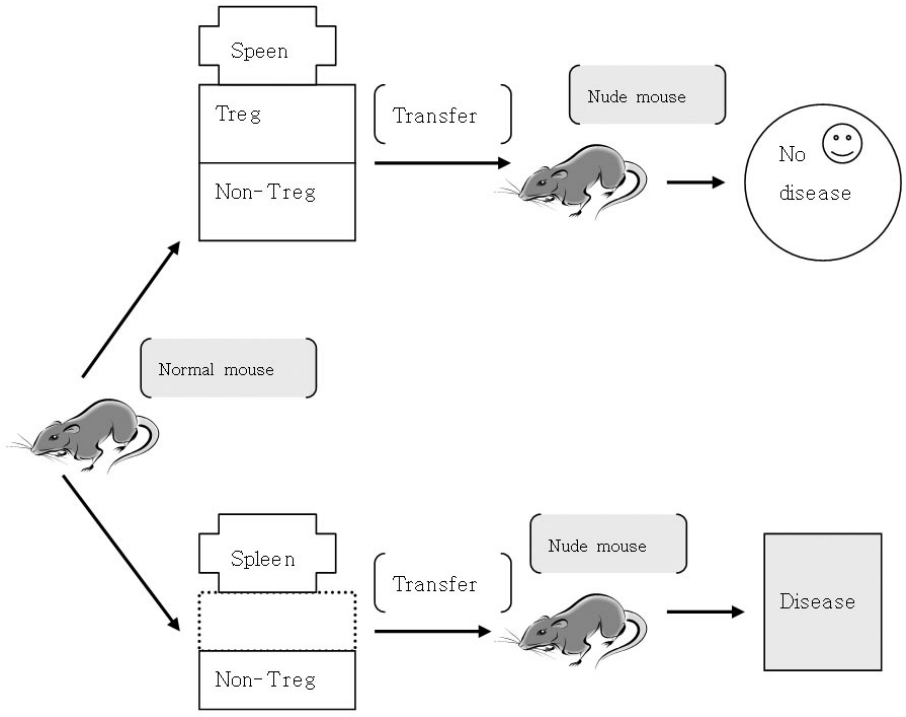

Figure 3. Suppressive roles of regulatory T cells in induction of autoimmune diseases. When thymocytes or splenic cell suspensions prepared from normal mice were transferred to syngeneic athymic nude mice, the recipients cause no autoimmune diseases. However, when thymocytes or splenic cell suspensions prepared from normal mice are depleted regulatory T cells (Treg) and remaining T cells are transferred to syngeneic athymic nude mice, the recipients spontaneously develop a variety of autoimmune diseases such as gastritis, oophoritis, orchitis, and thyroiditis, etc. (See test for details).

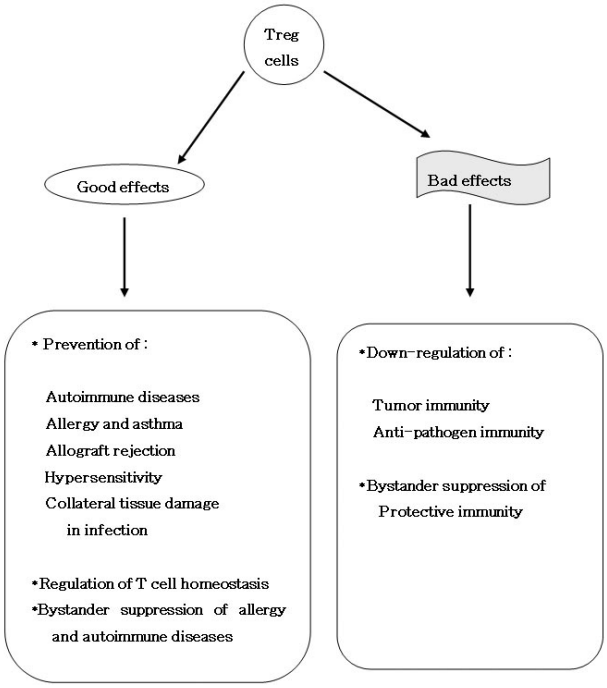

Figure 4. Beneficial and detrimental effects of regulatory T cells.

in decreased severity of CIA (72). It is interesting that the administration of the vasoactive intestinal peptide (VIP), an immunosuppressive antiarthritic neuropeptide, to arthritic mice resulted in the expansion of CD4+CD25+ Foxp3+ Treg cells in the periphery and joints, which inhibited delayed type hypersensitivity and autoreactive T cell activation and expansion, and that the VIP-generated CD4+CD25+ Treg cell transfer suppressed and significantly ameliorated the progression of CIA, indicating that the generation of highly efficient Treg cells by VIP *ex vivo* could be used as an attractive therapeutic tool (135-138). Furthermore, recently, Delgado *et al* have shown that treatment of lentiviral vectors expressing VIP (LentiVIP) also induced the generation and activation of CD4+CD25+Foxp3+ Treg cells in arthritic mice, indicating that VIP gene transfer may be a potential novel, effective treatment of RA and other chronic autoimmune diseases (139). Nguyen *et al* have shown that CD4+ Foxp3+ Treg cells are involved in constraining the immune phase of disease, as well as limiting the articula damage provoked by the pathogenic autoantibodies in terms of severity and of the range of affected joints which may contribute to the limited distal predominance of many arthritis (73). These studies suggest that Treg cells are important in the immune balance that culminates in arthritis.

Broere *et al* have shown that both oral and nasal application of cartilage proteoglycan could induce functional CD4+regulatory T cells in the chronic arthritis model, and transfer of CD4+ spleen cells from mucosally tolerized donor into proteoglycan-immunized mice abolished arthritis and reduced humoral responses, indicative of regulatory T cells with the capacity to inhibit already induced immune responses (140). An enzyme, indolamine 2,3-dioxygenase (IDO) degrades the essential amino acid tryptophan, can be synthesized by a many cell types and involved in the control of many immunological processes, such as tumor resistance, chronic infection, autoimmunity and allergic inflammation. The current work presented by Park and colleagues provides further understanding on mechanisms underlying oral tolerance induction by showing that IDO-expressing DCs located in the gut are involved in the inhibition of T-cell response and the generation of CD4+CD25+ Treg cells (70). They showed that CD11c+DCs in Peyer's patches induce the generation of collagen type II-specific CD4+CD25+FOXP3 Treg cells from highly purified CD4+CD25- T cells in an IDO-dependent manner, indicating IDO-producing DCs and CD4+CD25+ Treg cells may form a positive feedback loop in he induction of oral tolerance.

Interestingly, in one human study, frequencies of CD4+ $CD25^{high}$ Treg cells were significantly higher in the third trimester compared to 8 weeks post partum in patients with RA and controls and numbers of CD4+$CD25^{high}$ Treg cells inversely correlated with disease activity in the third trimester and post partum. This study strongly indicates that the amelioration of disease activity in the third trimester corresponded to the increased number of Treg cells and the pregnancy related quantitative and qualitative change of Treg cells suggest a beneficial effect of Treg cells on disease activity (141).

There is a large body of data in the literature demonstrating that RA patients have defective CD4+CD25+ Treg cells and increased osteoclastogenesis. Recently, it has been reported that activated CD4+CD25+ Treg cells improve clinical symptoms of CIA, regulate cytokine production and inhibit osteoclastogenesis *in vitro* and *in vivo* (142). Moreover, in several human studies, when examined in conventional *in vitro* assay, synovial CD4+CD25bright T cells in the patients with chronic rheumatic disease are able to suppress the proliferation of autologous CD4+CD25- (responder) T cells of synovial and peripheral origin (66,67). Synovial CD4+CD25+ T cells display an even increased suppressive capacity com-

pared with blood CD4+CD25+ T cells in RA and in juvenile idiopathic arthritis (64). In CIA, depletion of CD4+CD25+ T cells accelerates the onset of severe disease, and transfer of syngeneic CD4+CD25+ T cells into Treg cell-depleted mice reverses the increased severity (58,72). One study showed that in arthritic joints, synovial fluid of patients with different rheumatic diseases such as undifferentiated arthritides, systemic rheumatic diseases and reactive arthritis, 95% of the patients had a higher frequency of $CD25^{bright}CD4+$ T cells in synovial fluid as compared with peripheral blood (69). Thus, local expansion in the CD4+CD25+ Treg cell population in the rheumatoid synovium might reflect a mechanism for resolving the inflammatory immune response. And CD4+CD25+ Treg cells in the inflamed rheumatoid synovium might be important for a down-regulation of the inflammation, thereby delaying further tissue damage and impeding erosive inflammation. Furthermore, interestingly, Behrens *et al* have shown, in human RA, the efficacy of autologuous Treg cells in reducing inflammatory activity of synovial tissue cell cultures *ex vivo*, while in the synovium Foxp3+ Treg cells of patients with RA are reduced compared with peripheral blood and synovial fluid, suggesting that this local imbalance of Th1 and Treg cells may be responsible for repeated rheumatic flares and thus will be of interest as a target for treatments (68).

Almost all current therapeutic concepts in autoimmune diseases are based on the systemic suppression of immune functions and are not curative. It is evident, however, that only the elimination of the cells secreting inflammatory mediators, rather than in the blockade of secreted molecules, will offer real specific therapeutic advantages in the future. Thus, direct and specific cell therapy of RA will become a true alternative to conventional therapies (143). Indeed, emerging treatment paradigms such as autoantigenic peptides and cellular therapies are providing hope for a future in which immunopathology can be specifically and vigorously curtailed.

Autoimmune diabetes

Recent studies have provided convincing evidence that insulin-dependent diabetes mellitus (IDDM) or type 1 diabetes (T1D) is caused by an autoimmune destruction of pancreatic β cells, and inbred nonobese diabetic (NOD) mice develop spontaneous autoimmune diabetes that resembles human T1D in many respects (75,79-81,83). It has been well established that diabetic process in NOD mice are regulated by a balance between diabetogenic T cells and regulatory T cells (83,89), and that a progressive defect in Treg cell function is, in part, responsible for T1D in Nod mice (76,79,81). It has been reported that CD4+CD25+ Treg cells inhibit diabetes development and protection against spontaneous disease can be achieved during the preinsulitis and established insultitis phase of T1D by adoptive transfer of islet-specific Treg cells (75,76,78,79,82,84). The adaptive/polyclonal regulatory cells, which can be readily generated from normal CD4 populations can reverse T1D shortly after onset and become established as oligonal memory cells that persist indefinitely (1 year) as functionally stable Foxp3+, CD25- memory cells that transfer protection against T1D (75). However, recently, it was reported that small number of pancreatic islet antigen-specific Treg cells were much more effective than polyclonal Treg cells in blocking and reversing diabetes in NOD mice and that islet peptide mimic-specific Treg cells can be expanded and used to prevent autoimmune diabetes in Treg cell-deficient NOD mice (79). These results provided a direct demonstration of the presence of autoantigen-specific Treg cells in the natural setting that can be applied as therapeutics for organ- specific autoimmunity. Currently, Tritt *et al* have shown that CD4+Foxp3+nTreg cells also regulate later events of diabetogenesis by preferentially localizing in the pancreatic environment where they suppress the accumulation and function of effector T cell and that nTreg cell functional potency and intra-pancreatic proliferative potential declines with age, in turn augmenting diabetogenic responses and disease susceptibility (76).

Interestingly, in human study, Tittanen *et al* investigated the peripheral blood mononuclear cells (PBMCs) from children with T1D and analyzed the effect of insulin treatment on Treg cells in children with T1D, and PBMCs were stimulated for 72 hr with bovine/human insulin. They found that the expression of Foxp3, CTLA-4 and ICOS mRNA in PBMCs stimulated with bovine or human insulin is higher in patients on insulin treatment than in patients studied before starting insulin treatment and the insulin-induced Foxp3 protein expression in $CD4+CD25^{high}$ cells is detectable in flow cytometry, indicating that treatment with human insulin activates insulin-specific regulatory T cells in children with newly diagnosed T1D (80).

Coxsackievirus B4 (CB4) infections have long been associated with the induction of T1D. Currently, Richer *et al* reported that Treg cells induced after CB4 infection in the presence of TGF-beta prevented T1D. Furthermore, they reported that the presence of these viral induced Treg cells correlated

with protection from T1D without altering the antiviral response. These experimental results described above have important implications not only for the basic understanding of Treg cell biology, but may also lead to an effective clinical therapy in autoimmune diabetes.

Chronic kidney disease

Glomerulonephritis, the commonest cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD), is thought of as immune mediated, while other forms of renal injury are often described as nonimmune. Recent data have shown that Treg cells are potent modulators of tissue injury and repair in renal diseases (87). Animal studies exploring the therapeutic effect of these cells raise the exciting possibility that strategies targeting these cell types may be effective in treating and preventing kidney disease in human. Wolf *et al* demonstrated that CD4+CD25+ T cells were shown to have a protective role in an animal model of anti-glomerular basement membrane (anti-GBM) disease and Treg cells are potent suppressors of anti-GBM glomerulonephritis (87). They administered 1×10^6 CD4+CD25+ Treg cells and then induced anti-GBM disease in mice with rabbit anti-mouse GBM antibody. Interestingly, mice given Treg cells had a dramatic decrease of glomerular damage as well as a marked decrease of CD4+ T cell, CD8+ cell, and macrophage infiltration, and had a markedly reduced hisotological and functional renal injury compared with mice given CD4+CD25- T cells. Tracking studies using green fluorescent protein (GFP)-labeled Treg cells showed that Treg cells localized in the renal-draining lymph nodes and spleen and not in the kidneys of nephritic animals. Treg cell-treated mice did not have reduced immune complex formation with the glomeruli, suggesting that Treg cells did not affect the initiating phase of renal injury, but directly reduced end-organ damage by limiting kidney-specific immune cell activation within regional lymph nodes.

In human disease, Salma *et al* demonstrated the evidence of antigen specific Treg cells in Goodpasture's syndrome, employing type IV collagen antigen (90). They reported that while the disease is active, collagen-specific T cells are inflammatory, but once the disease subsides, collagen specific T cells become regulatory, suggesting that in Goodpasture's disease regulatory CD25+ T cells play an important role in inhibiting the autoimmune response.

In a adiramycin nephropathy (AN), a mouse model of chronic proteinuric renal disease, Treg cells were created by retroviral gene transfer of Foxp3 to native T cells, Wang *et al* demonstrated that transduction of Foxp3-transduced T cells inhibits a regulatory phenotype in these T cells, and Foxp3-transduced T cells inhibit the proliferation of CD4+CD25- cells *in vitro*. Furthermore, transuded Treg cells or CD4+CD25+ T cells significantly reduce glomerular and interstitial injury and protected against renal functional and structural injury *in vivo* in this mouse model (88,89). These data indicate that Treg cells are able to use multiple mechanisms to suppress immune responses. Therefore, cellular therapy using Treg cells to reconstitute or strengthen regulatory function is an attractive option for many immune-mediated diseases. Importantly, gene therapy directed at the kidney has been difficult because of the problems of delivery of vector to the kidney. However, these results reported by Wang *et al* suggest that gene therapy by transduction of immune cells may overcome this barrier to treatment (89). Accordingly, while it is an exciting prospect that regulatory cell could be used to dampen or even prevent renal disease, greater understanding of this therapeutic strategy, the disease being treated, and vigorously designed clinical trials are required before these therapies can be applied generally to human with renal disease.

Experimental autoimmune encyphalomyelitis (EAE), Multiple sclerosis (MS) and Parkinson's disease

EAE is an inflammatory, autoimmune demyelinating disease of the central nervous system (CNS) and a mouse model of human multiple sclerosis (144). MS is a chronic inflammatory disease characterized by lymphocyte infiltration and inflammation of the CNS white matter (103-105). Treg cells have emerged as crucial players in the pathogenic scenarios of CNS autoimmune inflammation. Targeted depletion of T cell causes spontaneous autoimmune disease in mice, whereas augmentation of Treg-cell function can prevent the development of or alleviate variants of EAE. It is interesting that Treg cells have the Janus face and a double-edged sword (13,52,104-106). It is well established that CD4+CD25+ Treg cells have the capability to prevent the development of EAE and have a major role in the natural recovery from actively-induced EAE (93,103-105,144). Kohm *et al* have shown that *in vitro*, Treg cells effectively could inhibit both the proliferation of and cytokine production by CD4+ T cell-dependent myelin oligodendrocyte glycoprotein (MOG)-specific Th1 cell, and *in vivo*, adoptive transfer of Treg cells conferred significant protection from clinical EAE, suggesting that CD4+CD25+ Treg cells suppress antigen-specific autoreactive immune response

and CNS inflammation during active EAE (98,144). Currently, Selvaraj *et al* have examined the immunomodulatory properties of iTreg cells in MOG-induced-EAE (MOG-EAE) and demonstrated that adoptive transferred iTreg cells were as potent as natural Foxp3+ Treg cells in preventing EAE development. These data demonstrate that iTreg cells are a capable surrogate for nTreg cells in immunotherapy of autoimmune encephalitis (92).

Immunity to *Salmonella* is typically Th1 cell dependent. Consequently, Th1 cell-dominating responses are also elicited when using conventional *Salmonella* vaccine vector (93). It is very interesting that the experimental *Salmonella* vaccine expressing colonization factor Ag 1 (*Salmonella* CFA/1 vaccine) possess anti-inflammatory properties and, when mice were given a single oral dose therapeutically, increases level of CD4+CD25+Foxp3+CD4+ Treg cells and reduces further development of EAE in SJL mice and that adoptive transfer of the vaccine-induced Treg cells protects mice against EAE with greater potency than naive or Samonella vector-induced Treg cells (93). Furthermore, oral treatment of EAE-induced SJL mice with the intracellular component *Salmonella* CFA/1 vaccine (*Salmonella* $CFA1_{IC}$) greatly reduced clinical disease of EAE together with increased IL-13 production. Importantly, these Treg cells elicited with *Salmonella* $CFA/1_{IC}$ vaccine could induce high potency by simply vaccinating against irrelevant antigens, offering a novel approach to treat autoimmune diseases independently of the autoantigen (157). Recently, a gene-therapeutic approach that increases CD4+ CD25+ Treg -cell potency by antigen-specifically redirecting them against pathologic T cell was developed (95).

Therapeutic cells are transgenetically modified with a chimeric receptors that link antigen-MHC extracellular and transmembrane domains with the cytoplasmic signaling tail of T cell receptor ζ. It was also demonstrated that CD4+CD25+ T cells or CD4+CD25+receptor-modified T cells expressing MBP prevented and treated EAE induced with MBP.

Midkine (MK), a heparin-binding growth factor, exerts pleiotropic effects,, including cell proliferation, cell migration, angiogenesis and fibrinolysis, in a variety of tissues. MK also plays important roles in the induction of oncogenesis, inflammation, and tissue repair. Furthermore, MK expression is up-regulated in the spinal cord during the induction and progression phases of EAE (96). Currently, Wang *et al* have shown that MK deficiency attenuates MOG-induced EAE because of an expansion of the Treg cell population in the peripheral lymph nodes, followed by decreases in the number of autoreacive Th1 and Th17 cells. Moreover, administration of anti-MK RNA aptamers that effectively neutralize MK induced expansion of the Treg cell population and reduced the symptoms of EAE, strongly suggesting that MK is a critical suppressor of Treg cell expansion and inhibition of MK using RNA aptamers may be a potent therapeutic strategy against autoimmune diseases, including MS (96). Recently, the U.S. Food Drug Administration approved anti-vascular endothelial growth factor aptamer as the treatment of age-related macular degeneration (145). The experimental results reported by Wang *et al* also provide strong evidence for the clinical efficacy of RNA aptamers (96). In addition, treatment of mice with VIP significantly reduced incidence and severity of EAE in a MS-related rodent model system and VIP suppressed EAE neuropathology by reducing CNS inflammation. Moreover, VIP treatment was therapeutically effective in established EAE, suggesting VIP also represents a novel multistep therapeutic approach for the future treatment of human MS.

In several current human studies, Venken *et al* demonstrated that patients with relapsing-remitting multiple sclerosis (RR-MS) show a suboptimal CD4+CD25+ Treg cell function, whereas no Treg cell alterations are observed in secondary progressive MS(SP-MS) patients. They analyzed the functional capacity and homeostatic parameters of naïve CD4+CD25+ $CD127^{low}$CD45RA+ Treg (nTreg) cell and their memory counterparts CD4+CD25+$CD127^{low}$ CD45RO+ Treg (mTreg) cells in untreated MS patients and healthy controls with the purpose to clarify the difference in Treg cell activity between early and chronic disease stage (146). They found that chronic MS patients had increased numbers of mTreg cells as compared with age-matches early MS patients, whereas nTreg cell frequencies did not differ significantly. TCR excision circle numbers were reduced in nTreg cells of early MS patients, suggestive of a diminished nTreg cell thymic output. Additionally, they reported that early MS patients showed a more restricted nTreg and mTreg cell gene profile. Finally, they provide strong evidence for disturbed nTreg cell development and function in MS patients (146). Venken *et al* also showed that Treg cells are functionally impaired in patients with RR-MS and that aberrant FOXP3 expression at the single-cell level correlated with Treg cell dysfunction in RR-MS patients (102). The intracellular expression of the programmed death receptor 1 (PD1) identifies a subset of naïve Treg cell with enhanced suppressive ability, and antigen stimulation results in the surface expression of PD1. Saresella *et al* examined naïve PD1- and PD1+ Treg cells in peripheral blood and cere-

brospinal fluid (CSF) of RR-MS patients and of healthy control subjects (103). They showed several important findings that CSF PD1- Treg cells were significantly augmented in MS patients and PD1-Treg cell were significantly increased in the peripheral blood of patients with stable disease compared to those with acute MS, and in patients responding to glatiramer acetate compared to acute- and drug-unresponsive patients. In addition, PD1+ Treg cells were similar in CSF and peripheral blood of all groups examined. The data suggest that PD1- Treg cell play a pivotal role in MS and offer a biological expansion for disease relapse (103).

Parkinson's disease, second in incidence to Alzheimer's disease is a progressive neurodegenerative disorder characterized by progress loss of substantia nigra pars compacta (SNpc) dopaminergic neurons and their projections to the caudate-putamen (147). Surprisingly, Reynolds *et al* have shown that CD4+CD25+ Treg cells have neuroprotective activities in an animal model of Parkinson's disease. These results support the use of therapeutic strategies, which induce Treg cell response to attenuate neurodegeneration and inhibit dopamineric neurodegeneration associated with Parkinson's disease (147).

Systemic lupus erythematosus (SLE)

SLE is a systemic autoimmune disease characterized by a wide spectrum of clinical manifestations, the loss of tolerance to self-antigens and the production of autoantibody (109,113,114). Some studies have shown that in SLE the number of circulating Treg cells may be decreased during active disease, and that the extent of such decrease may correlate with severity of the disease (113,179). Recent data in murine models of lupus have suggested the possibility to target Treg cells for the modulation of SLE, and Treg-based intervention has been proposed as a novel therapeutic mean for a better management of the disease (113-115). Injecting lupus prone (SWRxZNB)F1 mice with 1 μg nucleosomal histone peptide autoepitopes subcutaneously induced potent CD4+CD25+ and CD8+ Treg cells that were effective in suppressing lupus autoimmunity without causing allergic/anaphylactic reactions or generalized immunosuppression and repaired regulatory defect in SLE upon adoptive transfer *in vivo* (112). These Treg cells are not only efficient in suppressing autoantigen recognition and autoantibody production, but they also inhibit migration/accumulation of pathogenic autoimmune cells in the target organ such as the kidney of mice prone to develop lupus nephritis (109,110).

In several human studies, it has been suggested that Treg cells are decreased in patients with SLE (107,108,111,115). Valencia *et al* demonstrated that a significant decrease in the suppressive function of $CD4+CD25^{high}$ Treg cells from peripheral blood of patients with active SLE as compared with normal donors and patients with inactive SLE. Notably, Treg cells isolated from patients with active SLE expressed reduced levels of Foxp3 mRNA and protein and poorly suppressed the proliferation and cytokine secretion of CD4+ effector T cells *in vitro* (115). This report may provide evidence that a reversible defect in Treg cell function in patients with active SLE and suggest that strategies to enhance the function of these cells might benefit patients with this autoimmune disease. Interestingly, glucocorticoid treatment enriched $CD4+CD25^{high}$ Treg cells in patients with SLE (107,111) and upregulated expression of FOXP3 in patients with asthma (148).

Inflammatory bowel disease (IBD)

The IBD, which include Crohn's disease and ulcerative colitis, are chronic inflammatory disorders affecting 0.3% of the Western population. Many different pathways contribute to the maintenance of tolerance to harmless antigens in intestine. When these important pathways are compromised, chronic intestinal inflammation can develop. Particularly, Treg cells have been shown to play an important role in the prevention and cure of colitis in animal models of intestinal inflammation (118). Mottet *et al* provided the first evidence that established colitis could be cured by treatment with CD4+CD25+ Treg cells, resulting in resolution of the lamina propria infiltrate in the intestine and reappearance of normal intestinal architecture. Treg T cells were found to be proliferated in the mesenteric lymph nodes and inflamed area (119). Additionally, recent data showed that Treg cells can prevent colitis by inhibiting the accumulation of tissue-seeking effector cells and that Treg cell accumulation in the intestine is dispensable for colitis suppression (120). In patients with active Crohn's disease FOXP3+CD4+ Treg cells are expanded in mucosal lymphoid tissues (lamina propria and mesenteric lymph nodes) but are decreased in the peripheral blood and they accumulates in areas of active inflammation, including granulomas and retain potent regulatory activity *ex vivo* (117). Interestingly, parenteral injection of filamenous hemagglutinin of *Bordetella pertussis* into SCID mice suppressed Th1 cells and pro-inflammatory cytokines and ameliorate disease activity in a chronic T cell-dependent model of colitis, suggesting filamentous hemagglutinin is a promising

partly responsible for the acute toxic effects of SAgs (149). *Staphylococcus* aureus enterotoxins (A, B, C, D, E, and toxic shock syndrome toxin) are the prototypic SAgs (149-152). Recently, increasing evidence suggest that SAgs play a important role in immune-mediated disease and SAgs abrogate nTreg cell activity. SAgs administration is able to significantly enhance ineffective anti-tumor immune response, resulting in potent and long-lived protective and anti-tumor immunity (149,151). Thus, understanding the events that control suppressive function of Treg cells may allow manipulation of these cells to inhibit or enhance their function in the development of novel therapies for autoimmune and allergic diseases, anti-tumor immunity, transplant rejection and other immune-mediated diseases (151). These results indicate that combining the transfer of Treg cells along with that of immunomodulated DC could well substantially improve the potential of Treg cell therapy (152).

Rapamycin

Rapamycin (sirllimus), a macrolide antibiotics produced by *Streptomyces hygroscopicus*, is a new effective drug used to prevent allograft rejection. Similarly to the immunosuppressants FK506 and cyclosporine A, rapamycin exerts its effect by binding to the intracellular immunophilin FK506-binding protein (FKBP12). However, unlike FK506 and cyclosporine A, rapamycin does not inhibit TCR-induced calcineurin activity. Rather, the rapamycin-FKBP12 complex inhibits the serine/threonine protein kinase called mammalian target of rapamycin (mTOR), the activation of which is required for protein synthesis and cell-cycle progression. Therefore, rapamycin blocks signaling in response to cytokines, whereas FK560 and cyclosporin A exert their inhibitory effects by blocking TCR-induced activation (153). Accumulating data have provided evidences that rapamycin selectively expands CD4+CD25+Foxp+ Treg cells and expanded Treg cells suppress proliferation of syngeneic T cells *in vitro* and *in vivo* and prevent allograft rejection *in vivo*. Interestingly, rapamycin does not block activation-induced cell death and proliferation of CD4+ T cells *in vitro*, suggesting rampamycin can be used to expand Treg cells for *ex vivo* cellular therapy in T-cell mediated diseases (154). Moreover, the capacity of rapamycin to allow growth of functional CD4+CD25+FOXP3+ Treg cells in healthy and type 1 diabetic patients, but also to deplete T effector cells, can be exploited for the design of novel and safe *in vitro* protocols for cellular immunotherapy in T cell-mediated diseases (155).

Vasoactive intestinal peptide (VIP)

As described above in RA and CIA, administration of VIP to mice resulted in expansion and generation of CD4+CD25+ Foxp3+ Treg cells in the periphery and joints and the VIP-generated Treg cell transfer suppressed and significantly ameliorated the progression of chronic autoimmune diseases (135-139). Accordingly, VIP can be used for the Treg cell therapy for immune-mediated diseases.

Midkine (MK)

As MK, a heparin-binding growth factor is a critical suppressor of Treg cell expansion and inhibition of MK using RNA aptamers may be a potent therapeutic strategy against autoimmune disease (96).

Statins

The statins, a group of inhibitors of the 3-hydrooxy-3-methylglutaryl coenzyme A reductase, are reported to influence a variety of immune system activities. Actually, the statins are used extensively in medical practice because of their ability to reduce cardiovascular mortality and stroke (156). Although this protective activity was initially ascribed to inhibition of cholesterol biosynthesis, it is now evident that statins are pleiotropic drugs with immunomodulatory and anti-inflammatory properties. In particular, statins treatment increased the percentage of Treg cells at inflammatory sites and in regional tissue-draining lymph nodes (156).

Therefore, this drug may be useful for Treg cell therapy.

CONCLUSION

It is now clear that Treg cells play a central role in maintaining peripheral tolerance to self-antigen and in regulating the immune response to non-self antigens. It almost goes without saying that although defining the Treg-cell mode of action is of great academic importance, it is also essential to develop effective approaches for the clinical manipulation of Treg cells. In addition, it seems probable that a clear understanding of how Treg cell work will present definitive opportunities for successful therapeutic intervention. Although FOXP3 appears to be required for human Treg cell development and functions, expression of FOXP3 alone is clearly not sufficient for regulatory function, as a significant percentage of human activated T cells express FOXP3 but not possess regulatory activity. Therefore, further studies are required and

Table I. Target of therapeutic strategies of regulatory T cell therapy in immune-mediated diseases

Disease	Therapeutic strategies	Concerns
Cancer and infection	Depletion of Tregs Inhibition of Treg homing Inhibition of Treg function	Induction of autoimmunity
Autoimmune disease, allergy, transplantation and infection	Induction of antigen-specific Treg *in vivo* Boosting of endogenous Tregs Adoptive transfer of Tregs	Increase susceptibility to infection Risk of tumor development

Tregs: Regulaory T cells

future studies should aim (1) at identifying new markers and new relevant genes linked to FOXP3, (2) studying the effect of current and new drugs used for the treatment of autoimmune disease, allergy, tumor and transplant rejection. The cautious and scientific manipulation of Treg cells for therapeutic purposes promises to be a burgeoning field of investigation, with the potential for a wide spectrum of clinical application. A new potent Treg cell therapy will be available for the treatment of autoimmune diseases, and it might be even be an adjunct therapy for various diseases with some specific drugs. This exciting area may be an area of personalized medicine that is not being adequately addressed by the pharmaceutical industry. The discovery of more specific surface biomarkers for Treg cells is imperative, as this will undeniably facilitate our ability to monitor Treg cellular frequency and function in the context of a given disease and will serve to determine the clinical effectiveness of novel therapeutic strategies destined to modulate Treg function *in vitro* (Table I). I believe that these regulatory cells may represent a kind of master switch, and by understanding how they are made, how they function and how they survive, we may be able to stop disease from occurring.

ACKNOWLEDGEMENTS

I thank Prof. Byron H, Waksman (School of Medicine, Yale University) who kindly taught me this exciting field of immunology and for his continuous encouragement. I also thank Prof. Hern-Ku Lee (Chonbuk National University Medical School) for helpful critical reading of the manuscript. I apologize to the many authors whose important research could not be cited because of space limitations.

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