REVIEW

Arch. Immunol. Ther. Exp., 2007, **55**, 151–159
PL ISSN 0004-069X

DOI 10.1007/s00005-007-0024-8

Trafficking of FoxP3$^+$ regulatory T cells: myths and facts

Chang H. Kim

Department of Comparative Pathobiology, Purdue Cancer Center, Purdue University, West Lafayette, IN 47907, USA

Received: 2007.01.07, **Accepted:** 2007.02.22, **Published online first:** 2007.06.08

Abstract

Fork head box P3 (FoxP3$^+$) regulatory T cells (Tregs) are specialized T cells for prevention of hyperimmune responses and autoimmunity. Tumors and pathogens can hijack FoxP3$^+$ Tregs to evade host immune responses. There is an increasing body of evidence that trafficking of FoxP3$^+$ Tregs is important for their effective suppression of target cells. Because of their distinctive functions and gene expression phenotype, the migratory behavior of FoxP3$^+$ Tregs has been somewhat mystified. The myths are that they have unique trafficking receptors and migratory behaviors that are different from those of conventional T cells. Another related myth is that FoxP3$^+$ regulatory T cell subsets have a fixed trafficking behavior from the time they are generated in the thymus. The recent progress in trafficking receptors and migratory behavior of FoxP3$^+$ Tregs is reviewed here and the validity of these myths is examined.

Key words: FoxP3, regulatory T cells, migration, chemokine receptor, integrin, selectin.

Abbreviations: 2^o LT – secondary lymphoid tissues, non-LT – non-lymphoid tissues, PP – Peyer's patches, IPEX – immunodeficiency polyendocrinopathy enteropathy X-linked syndrome, Tregs – regulatory T cells, FoxP3 – Fork head box P3, DP – double positive, SP – single positive.

Corresponding author: Dr. Chang H. Kim, Laboratory of Immunology and Hematopoiesis, Department of Comparative Pathobiology, Purdue University, 725 Harrison Street, West Lafayette, IN 47907, USA, tel.: +1 765 494-09-76, fax: +1 765 494-98-30, e-mail: chkim@purdue.edu

INTRODUCTION

Fork head box P3 (FoxP3$^+$) T cells are the most extensively characterized regulatory T cells (Tregs) with suppressive functions. Some call these cells "suppressor T cells". More commonly, these T cells are also called "Tregs". However, the term "Tregs" is inaccurate in that many Tregs with suppressive functions do not express FoxP3. Examples of these regulatory T cell subsets defined independently of FoxP3 expression are interleukin (IL)-10-generated Tregs (Tr1) [39] and transforming growth factor (TGF)-β1-generated Tregs (Th3) [18, 121]. This, however, does not necessarily mean that Tr1 and Th3 cells are FoxP3$^-$. Moreover, some people include Th1 and Th2 cells in the category of Tregs. For simplicity, we will use the term "FoxP3$^+$ T cells" to refer to the Tregs that express FoxP3 and that are often defined by the surrogate markers CD4 and CD25. However, the readers should note that it is unavoidable, sometimes, to use the terms "CD4$^+$CD25$^+$ T cells" and "Tregs" to refer to phenotypically or functionally related but incompletely characterized T cell subsets described in the literature.

This review starts with the basic biology of FoxP3$^+$ T cells and T cell trafficking in general, followed by more detailed discussion on trafficking of FoxP3$^+$ T cells. The focus of this review will be on the two separate trafficking receptor switches of FoxP3$^+$ T cells occurring in the thymus and secondary lymphoid tissues (2^o LT). As mentioned in the abstract, the validity of the myths on trafficking of FoxP3$^+$ T cells will be examined at the conclusion of this review.

FUNDAMENTALS OF THE FoxP3$^+$ T CELL BIOLOGY

The activity of T cells that can suppress immune responses was described many decades ago. It was not until 1995 that the CD4$^+$ T cell subset highly enriched with suppressor T cells was isolated utilizing CD25 as a cell surface marker [90]. Since then, it has been demonstrated by many groups that the CD4$^+$CD25$^+$ T cells have suppressive activities on autoimmunity [89], graft rejection [113], and humoral and cell-mediated immune responses [88, 106, 122]. It has been reported that CD4$^+$CD25$^+$ T

cells are deficient in many autoimmune or inflammatory diseases, while they are enriched in tumors or in infection by some pathogens [89]. Tumors and pathogens can recruit or induce the generation of $CD4^+CD25^+$ or $FoxP3^+$ T cells to evade hostile immune responses [11].

The discovery that scurfy mice and patients with immunodeficiency polyendocrinopathy enteropathy X--linked syndrome (IPEX) have loss-of-function mutations in the FoxP3 gene (*FoxP3)* led to the discovery that FoxP3 is the key protein that programs the development and function of the $CD4^+CD25^+$ Tregs [9, 14, 49, 83, 107, 110]. IPEX is also called "X-linked autoimmunity and allergic dysregulation" (XLAAD). Indeed, the majority of $CD4^+CD25^+$ Tregs in the thymus and 2^o LT express FoxP3 protein [30, 86, 108]. FoxP3 is a transcription factor that can act as a transcription repressor [10, 71, 94, 114]. FoxP3 can modulate the function of NFAT and NF-κB, transcription factors that regulate the expression of many genes induced in activated T cells. Enforced expression of FoxP3 in mouse T cells by retroviral gene transfer turned normal T cells into suppressor T cells [29, 41]. Ectopic expression of FOXP3 (written in all capital letters for the human protein versus FoxP3 for the mouse protein) in human T cells led to similar results, but complete conversion into functionally competent Tregs was not achieved, suggesting potential involvement of additional factors in the process [1].

The generation of $FoxP3^+$ $CD4^+$ cells is substantially delayed relative to $FoxP3^-$ $CD4^+$ thymocytes during their development [28]. $FoxP3^+$ T cells are generated as $CD4^+CD8^+$ DP cells and $CD4^+$ single-positive (SP) cells in the thymus [28, 108], and the thymus-generated $CD4^+$ $FoxP3^+$ T cells have the naïve phenotype in many aspects [65]. Thymus-generated $FoxP3^+$ T cells have high-affinity T cell receptors (TCRs) to self antigens [47]. Therefore, these T cells are thought to be a major player in suppressing self-reactive T cells. $CD4^+$ $FoxP3^+$ T cells can be induced in the periphery during immune responses to foreign antigens [60]. This would probably occur during T cell activation by antigen-presenting cells. Activation of naïve human T cells induces FOXP3, but this expression is transient and most resting T cells do not retain the FOXP3 expression [74, 107]. Small numbers of T cells retain the FOXP3 expression after T cell activation and become $FOXP3^+$ Tregs. The conversion rate from $FoxP3^-$ to $FoxP3^+$ cells is very low in mice compared with human T cells [65]. $CD8^+$ $FoxP3^+$ T cells exist, but are rare in the thymus and periphery, and they can be induced in certain conditions in a manner similar to $CD4^+$ $FoxP3^+$ T cells [12, 73].

$FoxP3^+$ T cells can suppress various immune cells, such as CD4, CD8, CD1d-restricted NKT, NK, monocytes, dendritic, and B cells [6, 17, 68, 84, 96, 100, 102]. The mechanisms of suppression are still incompletely understood. $FoxP3^+$ T cells can suppress target cells with TGF-β, IL-10, CTLA-4, and heme oxygenase-1 [4, 19, 35, 37, 38, 75, 80, 81, 92, 120]. $FoxP3^+$ T cells express granzymes and can kill target cells in a perforin-dependent and independent pathways *in vitro* [35, 38, 120]. $FoxP3^+$ T cells express TGF-β and/or IL-10 to suppress target cells [79, 119]. $FoxP3^+$ T cells highly express CTLA-4 and suppress B7-expressing antigen-presenting cells in an IDO-dependent manner [37]. Carbon monoxide produced by heme oxygenase-1 may suppress target cells [81, 92]. It is clear that these mechanisms operate in certain *in vitro* conditions, but their validity *in vivo* remains controversial.

BASICS OF T CELL TRAFFICKING AND TRAFFICKING RECEPTORS

Two classes of trafficking receptors regulate T cell trafficking to various tissue sites [15, 50]. These are adhesion molecules and chemoattractant receptors. The two types of receptors work together in trafficking of T cells. Adhesion molecules mediate the initial loose interaction between T cells and endothelial cells, called "rolling", and the subsequent "firm adhesion" before "diapedesis" through endothelial cells. To advance from rolling to firm adhesion, T cells have to be activated by chemokines expressed on the endothelial cell surface. There are ~40 chemokines identified so far, and these chemokines can activate chemokine receptors (~20 identified) expressed on leukocytes. This activation, in turn, activates integrins for firm adhesion of T cells to the endothelial cell surface. Chemokines also induce directional migration (chemotaxis) of T cells [20, 46, 52]. Expression of chemokines in tissue is tightly controlled by cytokines and other environmental factors [50].

In the thymus, early T cell progenitors reside in the cortex and differentiate to $CD4^+CD8^+$ DP and then to $CD4^+$ or $CD8^+$ SP T cells [85]. At the same time, T cells undergo selection processes to delete many T cells with nonfunctional TCRs (positive selection) or TCRs that react strongly against self antigens (negative selection) [97]. DP T cells are found in the cortex, while SP T cells are localized in the medulla and eventually emigrate to the blood circulation [85]. T cells undergo switches in expression of chemokine receptors during their development in the thymus and periphery. The expression of chemokine receptors by thymocytes is important for chemotactic attraction of thymocytes to other cell types in thymic microenvironments. CCR8 and CCR9 are expressed by early $CD4^-CD8^-$ double-negative thymic T cells [16, 55]. As the T cells become DP cells, they upregulate CXCR4 and become localized in the cortex. More mature SP T cells highly express CCR7 and are found in the medulla [16, 55]. Naïve T cells use CCR7 and CD62L to migrate into 2^o LT [98, 109]. The two receptors are also necessary for continuous circulation of naïve T cells between T cell areas and the blood circulation. Upon antigen priming, naïve T cells quickly up-regulate CXCR3 and CXCR5 [5], the chemokine receptors involved in T cell interaction with dendritic cells and in chemotaxis into B cell areas, respectively. T cells also up-regulate additional receptors, such as CCR4, CCR5, CCR2, CXCR6, CCR6, and CRTH2, for

migration to various non-lymphoid or inflammatory tissue sites [54].

Effector T cell subsets, such as Th1 and Th2 cells, express different chemokine receptors [13, 22, 56, 70, 91, 123]. Th1 cells often express CXCR3, CCR5, and CXCR6 (Th1 type), while many Th2 cells express CCR4, CCR8, and CRTH2 (Th2 type). Non-polarized memory T cells preferentially express CCR7 and CXCR5 [53, 56, 57]. Expression of the chemokines that bind Th1 or Th2 type receptors is tightly regulated by Th1 (IFN-γ) or Th2 (IL-4, IL-5, and IL-13) cytokines, respectively [2, 26, 93, 95], suggesting that Th1 and Th2 cells can migrate to different tissues in an amplified manner. CCR9 and the integrin α4β7 are involved in the migration of lymphocytes to the small intestine [21, 40, 61, 63, 77]. T cells use α4β7 to roll on the MadCAM-1 expressed on the surface of gut endothelial cells and use certain chemokine receptors such as CCR9 to trigger firm adhesion on endothelial cells. The CCR9 ligand CCL25 is specifically expressed on the crypt epithelium of the small intestine and attracts CCR9+ lymphocytes [62]. Although its function is unclear, the CCR10 ligand CCL28 is more broadly expressed in the large intestine and other mucosal tissue sites [63, 82].

GENERATION AND MIGRATION OF FoxP3+ T CELLS WITHIN THE THYMUS

Normal T cell development requires molecular interactions between developing thymocytes and the thymic epithelium at different locations of the thymus, and alterations of this highly coordinated process can result in defective T cell development, leading to either immunodeficiency or autoimmunity. It is believed that FoxP3+ T cells undergo the same highly regulated process to become functionally mature cells. As mentioned before, FoxP3+ T cells appear at DP and SP stages [28, 108], presumably after TCR activation for positive selection (Fig. 1). Almost all thymic FoxP3+ cells are found in the thymic medulla [28], which is in line with the fact that most thymic FoxP3+ cells are SP cells. DP FoxP3+ T cells highly express CXCR4 and CCR9, the chemokine receptors important for localization of DP T cells in the cortex [65]. In contrast, SP FoxP3+ T cells highly express CCR7, the chemokine receptor important for localization of T cells in the medulla and emigration to the blood circulation. Thus, FoxP3+ T cells undergo a chemokine receptor switch in the thymus, required for both intrathymic localization and emigration out of the thymus (Fig. 2).

THE TRAFFICKING RECEPTOR SWITCH IN 2º LT

The thymic FoxP3+ T cells that emigrate into the blood circulation uniformly express CD62L and CCR7

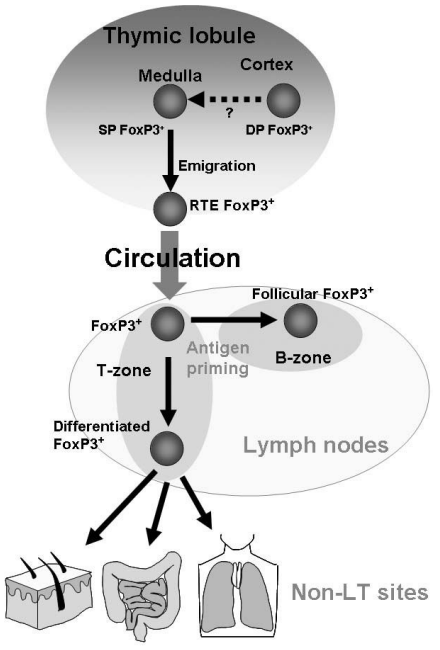

Fig. 1. Organ to organ migration of FoxP3+ T cells. FoxP3+ T cells are generated at the DP and SP stages in the thymus. Most FoxP3+ T cells are CD4 SP cells and are found in the medulla. After maturation in the thymus, SP FoxP3+ T cells emigrate to the circulation, becoming RTE (recent thymic emigrant) FoxP3+ cells. RTE FoxP3+ cells preferentially migrate to 2º LT for antigen priming. Dendritic cells present antigens to FoxP3+ cells in 2º LT for antigen priming and differentiation. This differentiation includes another trafficking receptor switch from secondary lymphoid to non-lymphoid homing receptors. Some FoxP3+ T cells become follicular FoxP3+ T cells to regulate B cells and follicular T-helper cells. Other FoxP3+ T cells emigrate to the circulation to migrate to non-LT associated with the 2º LT. This migration requires the expression of tissue-specific trafficking receptors.

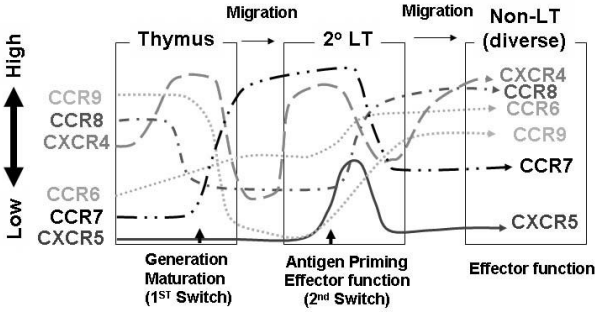

Fig. 2. Trafficking receptor switches of FoxP3+ T cells. There are largely two trafficking receptor switches: primary and secondary. The primary trafficking receptor switch occurs in the thymus. $CXCR4^{high}$ $CCR9^{high}$ $CCR7^{low}$ DP FoxP3+ cells become $CXCR4^{low}$ $CCR9^{low}$ $CCR7^{high}$ SP FoxP3+ cells. The FoxP3+ thymic emigrants almost exclusively migrate to 2º LT and become $CXCR4^{high}$ $CCR7^{high}$ cells. In 2º LT, these FoxP3+ T cells can undergo the second trafficking receptor switch. This involves down-regulation of lymphoid tissue homing receptors (L-selectin, CCR7, and CXCR4), but up-regulation of a number of memory/effector chemokine receptors (CCR2, CCR4, CCR5, CCR6, CCR8, CCR9, CXCR3, CXCR5 and CXCR6). Up-regulation of the latter group of trafficking receptors is required for migration into various non-lymphoid tissue sites. The second switch results in heterogeneous and distinct FoxP3+ T cell subsets in homing behavior.

[65, 67]. CXCR4 expression is dramatically reduced at the SP FoxP3+ T cell stage in the thymus, but it is regained in the periphery [65], suggesting a potential role of CXCR4 in FoxP3+ T cell localization in peripheral tissues. It is thought that CD62L mediates the rolling of FoxP3+ T cells on high endothelial cell venules [105], and the CCR7 expressed by FoxP3+ cells recognizes the CCL21 and CCL19 chemokine signals on the endothelial surface and activates integrins for firm adhesion. In 2° LT, most FoxP3+ T cells are localized in the T cell area [38]. This localization is the result of chemotaxis of CCR7+ T cells to the CCR7 ligands expressed in the T cell area of 2° LT [32, 50].

Once FoxP3+ T cells enter 2° LT and migrate into the T cell area, it is thought that FoxP3+ T cells seek the antigen signals provided by dendritic cells in a manner similar to other T cells. If there are no antigen signals, the T cells would emigrate the 2° LT and go back to the blood circulation. Upon encounter with dendritic cells presenting the right antigens, FoxP3+ T cells undergo a differentiation process that changes their trafficking receptors [65, 67]. As mentioned before, newly arrived FoxP3+ T cells in the 2° LT express L-selectin, CCR7, and CXCR4, which are uniformly expressed by naïve conventional T cells. These trafficking receptors are homing and retention receptors for T cells withing 2° LT. Upon antigen priming, CXCR5 is rapidly induced in many FoxP3+ T cells [69]. This trafficking receptor switch by FoxP3+ T cells is described in Fig. 2.

CXCR5 is the homing receptor for the B cell area of 2° LT [31]. The B cell areas of 2° LT can be classified into primary follicles and secondary follicles. Primary follicles are mostly composed of naïve B cells and become secondary follicles containing germinal centers during T cell-dependent immune responses. Germinal centers are filled with activated B cells undergoing differentiation to plasma cells and memory B cells [76]. Germinal centers have also activated T cells, called GC-T cells, and dendritic cells [58]. Moreover, the presence of follicular dendritic cells in germinal centers is an important indicator for the presence of germinal centers [66, 104]. CXCR5+ FoxP3+ T cells can migrate to the CXCR5 ligand CXCL13 [69]. In contrast, the expression of CCR7 and the response to the CCR7 ligands are rapidly decreased in the FOXP3+ T cells undergoing activation [65, 69]. The down-regulation of CCR7 and up-regulation of CXCR5 suggest that these FoxP3+ T cells would migrate into the B cell areas. These follicular FoxP3+ T cells are thought to be important for regulating humoral immune responses [51]. In mice, depletion of CD4+CD25+ T cells followed by an immunization with T cell-dependent antigens led to hyper-production of antibodies [24]. Similarly, depletion of FoxP3+ T cells followed by immunization with red blood cells greatly increased antibody-mediated autoimmune hemolytic anemia [78].

Other chemokine receptors that are commonly expressed by FoxP3+ T cells include non-lymphoid tissue homing receptors such as CCR4, CCR6, CCR8, and CXCR3 [33, 43, 59, 64, 67, 115]. The CCR4 chemokine ligands are produced by activated immune cells such as B cells and other tissue cells during Th2 immune responses [3, 56]. The CXCR3 chemokine ligands are produced by a variety of tissue cells and immune cells during immune responses and in inflammation [8, 13]. The CCR6 ligand CCL20 is produced by epithelial cells in mucosal tissues, including Peyer's patches (PP) [7, 27, 36, 59, 111]. The CCR8 ligand CCL1/I-309/TCA-3 is produced by mast cells and activated T cells and it attracts neutrophils, macrophages, and activated T cells [23, 72, 87, 103, 112]. Hence the up-regulation of these chemokine receptors on antigen--activated FoxP3+ T cells suggests that some FoxP3+ T cells differentiate into cells that can migrate to non--lymphoid or inflamed tissues [65]. Interestingly, FoxP3+ T cells are significantly more efficient than FoxP3– T cells in up-regulation of these non-lymphoid tissue homing receptors as the result of the second switch in trafficking receptors (Fig. 2). The second switch generates FoxP3+ T cells highly expressing non-lymphoid tissue-homing chemokine receptors. Consistently, antigen-primed FoxP3+ T cells can more efficiently migrate to non-lymphoid tissues (non-LT) than comparably antigen-primed FoxP3– CD4+ T cells [65]. This gives FoxP3+ T cells certain advantages in migrating to non-LT, which would be important for effective immune tolerance in the periphery.

ACQUISITION OF TISSUE-SPECIFIC MIGRATION ABILITIES BY FoxP3+ T CELL SUBSETS

One important feature of T cell migration is the homing of memory and effector T cells to the tissue type of initial antigen encounter. In other words, memory T cells, antigen-primed in the lymph nodes draining a tissue site, would migrate back to that tissue type rather than other tissue types. This homing behavior of T cells to sites of antigen encounter obviously has advantages over random migration in immune surveillance and effector function. This specific tissue tropism is determined by combinations of the trafficking receptors expressed by T cells. FoxP3+ T cells, antigen primed in mesenteric lymph nodes and PP, acquire CCR9 and α4β7 [65]. CCR9 is the homing receptor for the small intestine [116–118], while α4β7 is the homing receptor for the whole mucosal tissue system [25, 40]. In contrast, most FoxP3+ T cells, antigen primed in peripheral lymph nodes, lack the expression of CCR9 and α4β7, but highly express CCR8 [65]. It is the microenvironment-specific cue composed of cytokines, nuclear receptor agonists such as retinoic acid, and other unidentified factors that induce the tissue-specific expression of homing receptors in T cells. Retinoic acid, for example, plays a critical role in the induction of CCR9 and α4β7 in T cells [44]. Dendritic cells of gut tissues express the enzymes that turn serum retinol into retinoic

acid. Therefore, dendritic cells play key roles in generation of gut-homing T cells in mucosal tissues [44, 45, 77].

IMPACT OF THE MIGRATION CAPACITY OF FOX3+ T CELLS ON THEIR EFFECTOR FUNCTION

Through *in vitro* and *in vivo* studies, scientists have gained insights into the effector functions of FoxP3+ T cells. First, FoxP3+ T cells can suppress target cells only at close ranges involving cell-cell contact. Second, the relative ratio of FoxP3+ cells to target cells should be high enough for effective suppression. *In vivo*, it is the migration and expansion capacities of FoxP3+ T cells that would make them accessible to target cells in sufficient numbers. It has been reported that only secondary lymphoid tissue-homing ($CD4^+CD25^+CD62L^+$) FoxP3+ cells, but not non-lymphoid tissue-homing ($CD4^+CD25^+CD62L^-$) FoxP3+ T cells, were able to prevent graft-versus-host disease and autoimmune gastritis, diabetes, and colitis, induced by $CD45RB^{high}$ cells, in mice [34, 99, 101]. The difference in suppressive activities of the two FoxP3+ T cell subsets may be attributed to their difference in migratory capacities. Alternatively, they are different in their capacities in expansion or effector function. Currently, no evidence is available to support the possibility that non-LT-homing FoxP3+ T cells would have an effector function different from that of 2° LT-homing FoxP3+ T cells. However, there is evidence that 2° LT-homing FoxP3+ T cells are better than non-LT-homing FoxP3+ T cells in proliferation [34, 99, 101]. Certainly, FoxP3+ T cells of high proliferative potential would quickly give rise to sufficient numbers of progenies for effective suppression of target cells. Because of the ability to migrate into 2° LT, these FoxP3+ cells can also suppress the generation and expansion of inflammatory T cells at the antigen-priming step. After antigen priming in 2° LT, FoxP3+ T cells can gain the migratory capacity to non-LT. The 2° LT-homing FoxP3+ T cells may not be effective in controlling existing inflammation at effector sites, where effector T cells are already active in inducing inflammation. It is thought that non-lymphoid tissue-homing FoxP3+ T cells are required to efficiently suppress inflammation at the effector site. In this regard, non-LT-homing $CD4^+\alpha E^+$ Tregs, but not 2° LT-homing $CD4^+CD25^+CD62L^+$ T cells, can effectively suppress collagen-induced arthritis in mice [42]. It has been also demonstrated that the CCL5-CCR5 pathway is required for migration of FoxP3+ T cells into chronically inflamed intestine [48]. Blocking this pathway exacerbated the intestinal inflammation, supporting the important role of FoxP3+ T cell migration to effector sites for suppression of existing inflammation.

CONCLUDING REMARKS

The migratory ability of FoxP3+ T cells to the 2° LT is an important factor that determines their expansion and prevention of the generation of inflammatory T cells. The migratory ability of FoxP3+ T cells to non-LT is important for control of inflammation at the effector sites. It is time to examine the validity of the myths described in the abstract of this review.

Do FoxP3+ Tregs have cell-lineage-specific trafficking receptors that are different from those of FoxP3− T cells? The answer is no. They do not have unique trafficking receptors, but share many receptors with conventional T cells. However, FoxP3+ Tregs more homogeneously express non-LT homing receptors such as CCR5, CCR6, CCR8, and CXCR6 than do FoxP3− T cells. Also, tissue-specific homing receptors such as $\alpha4\beta7$ and CCR9 are preferentially expressed by gut-associated FoxP3+ T cells compared with FoxP3− T cells [65]. FoxP3+ Tregs can basically migrate to any tissue sites where FoxP3− T cells can migrate to. However, they can migrate more efficiently into major non-LT sites due, in part, to their high expression of the non-LT and tissue-specific homing receptors.

Do FoxP3+ Tregs have a predetermined (or fixed) trafficking behavior from the time they are generated in the thymus? The answer is again no. FoxP3+ Tregs undergo developmental switches in trafficking receptors in the thymus and 2° LT (Fig. 2). Through these differentiation processes, FoxP3+ T cells change their trafficking receptors and migratory behaviors to migrate sequentially to the right tissue sites where suppression of immune responses is required to maintain immune tolerance.

Acknowledgment: I thank Jeeho Lee, Hyung Lim, Seung Kang, and Chuanwu Wang in the laboratory of Immunology and Hematopoiesis at Purdue University for sharing their insights. This study was supported, in part, by grants from NIH-NIAID (AI063064), the Sidney Kimmel Foundation, and the American Heart Association to Chang H. Kim.

REFERENCES

1. Allan S. E., Passerini L., Bacchetta R., Crellin N., Dai M., Orban P. C., Ziegler S. F., Roncarolo M. G. and Levings M. K. (2005): The role of 2 FOXP3 isoforms in the generation of human CD4+ Tregs. J. Clin. Invest., **115**, 3276–3284.
2. Andrew D. P., Chang M. S., McNinch J., Wathen S. T., Rihanek M., Tseng J., Spellberg J. P. and Elias C. G. 3rd (1998): STCP-1 (MDC) CC chemokine acts specifically on chronically activated Th2 lymphocytes and is produced by monocytes on stimulation with Th2 cytokines IL-4 and IL-13. J. Immunol., **161**, 5027–5038.
3. Andrew D. P., Ruffing N., Kim C. H., Miao A., Heath H., Li Y., Murphy K., Campbell J. J., Butcher E. C. and Wu L. (2001): C-C chemokine receptor 4 expression defines a major subset of circulating non-intestinal memory T cells of both Th1 and Th2 potential. J. Immunol., **166**, 103–111.
4. Annunziato F., Cosmi L., Liotta F., Lazzeri E., Manetti R., Vanini V., Romagnani P., Maggi E. and Romagnani S. (2002): Phenotype, localization, and mechanism of suppression of CD4(+)CD25(+) human thymocytes. J. Exp. Med., **196**, 379–387.

5. Ansel K. M., McHeyzer-Williams L. J., Ngo V. N., McHeyzer-Williams M. G. and Cyster J. G. (1999): *In vivo*--activated CD4 T cells upregulate CXC chemokine receptor 5 and reprogram their response to lymphoid chemokines. J. Exp. Med., **190**, 1123–1134.
6. Azuma T., Takahashi T., Kunisato A., Kitamura T. and Hirai H. (2003): Human CD4+ CD25+ regulatory T cells suppress NKT cell functions. Cancer Res., **63**, 4516–4520.
7. Baba M., Imai T., Nishimura M., Kakizaki M., Takagi S., Hieshima K., Nomiyama H. and Yoshie O. (1997): Identification of CCR6, the specific receptor for a novel lymphocyte-directed CC chemokine LARC. J. Biol. Chem., **272**, 14893–14898.
8. Balashov K. E., Rottman J. B., Weiner H. L. and Hancock W. W. (1999): CCR5(+) and CXCR3(+) T cells are increased in multiple sclerosis and their ligands MIP--1alpha and IP-10 are expressed in demyelinating brain lesions. Proc. Natl. Acad. Sci. USA, **96**, 6873–6878.
9. Bennett C. L., Christie J., Ramsdell F., Brunkow M. E., Ferguson P. J., Whitesell L., Kelly T. E., Saulsbury F. T., Chance P. F. and Ochs H. D. (2001): The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat. Genet., **27**, 20–21.
10. Bettelli E., Dastrange M. and Oukka M. (2005): Foxp3 interacts with nuclear factor of activated T cells and NF--kappa B to repress cytokine gene expression and effector functions of T helper cells. Proc. Natl. Acad. Sci. USA, **102**, 5138–5143.
11. Beyer M. and Schultze J. L. (2006): Regulatory T cells in cancer. Blood, **108**, 804–811.
12. Bisikirska B., Colgan J., Luban J., Bluestone J. A. and Herold K. C. (2005): TCR stimulation with modified anti--CD3 mAb expands CD8+ T cell population and induces CD8+CD25+ Tregs. J. Clin. Invest., **115**, 2904–2913.
13. Bonecchi R., Bianchi G., Bordignon P. P., D'Ambrosio D., Lang R., Borsatti A., Sozzani S., Allavena P., Gray P. A., Mantovani A.and Sinigaglia F. (1998): Differential expression of chemokine receptors and chemotactic responsiveness of type 1 T helper cells (Th1s) and Th2s. J. Exp. Med., **187**, 129–134.
14. Brunkow M. E., Jeffery E. W., Hjerrild K. A., Paeper B., Clark L. B., Yasayko S. A., Wilkinson J. E., Galas D., Ziegler S. F. and Ramsdell F. (2001): Disruption of a new forkhead/winged-helix protein, scurfin, results in the fatal lymphoproliferative disorder of the scurfy mouse. Nat. Genet., **27**, 68–73.
15. Butcher E. C., Williams M., Youngman K., Rott L. and Briskin M. (1999): Lymphocyte trafficking and regional immunity. Adv. Immunol., **72**, 209–253.
16. Campbell J. J., Pan J. and Butcher E. C. (1999): Cutting edge: developmental switches in chemokine responses during T cell maturation. J. Immunol., **163**, 2353–2357.
17. Cederbom L., Hall H. and Ivars F. (2000): CD4+CD25+ regulatory T cells down-regulate co-stimulatory molecules on antigen-presenting cells. Eur. J. Immunol., **30**, 1538–1543.
18. Chen Y., Kuchroo V. K., Inobe J., Hafler D. A. and Weiner H. L. (1994): Regulatory T cell clones induced by oral tolerance: suppression of autoimmune encephalomyelitis. Science, **265**, 1237–1240.
19. Choi B. M., Pae H. O., Jeong Y. R. Kim Y. M. and Chung H. T. (2005): Critical role of heme oxygenase-1 in Foxp3--mediated immune suppression. Biochem. Biophys. Res. Commun., **327**, 1066–1071.
20. Cyster J. G. (2000): Leukocyte migration: scent of the T zone. Curr. Biol., **10**, R30–33.
21. Cyster J. G. (2003): Homing of antibody secreting cells. Immunol. Rev., **194**, 48–60.
22. D'Ambrosio D., Iellem A., Bonecchi R., Mazzeo D., Sozzani S., Mantovani A. and Sinigaglia F. (1998): Selective up-regulation of chemokine receptors CCR4 and CCR8 upon activation of polarized human type 2 Th cells. J. Immunol., **161**, 5111–5115.
23. Doyle H. A. and Murphy J. W. (1999): Role of the C-C chemokine, TCA3, in the protective anticryptococcal cell--mediated immune response. J. Immunol., **162**, 4824–4833.
24. Eddahri F., Oldenhove G., Denanglaire S., Urbain J., Leo O. and Andris F. (2006): CD4+ CD25+ regulatory T cells control the magnitude of T-dependent humoral immune responses to exogenous antigens. Eur. J. Immunol., **36**, 855–863.
25. Erle D. J., Briskin M. J., Butcher E. C., Garcia-Pardo A., Lazarovits A. I. and Tidswell M. (1994): Expression and function of the MAdCAM-1 receptor, integrin alpha 4 beta 7, on human leukocytes. J. Immunol., **153**, 517–528.
26. Farber J. M. (1997): Mig and IP-10: CXC chemokines that target lymphocytes. J. Leukoc. Biol., **61**, 246–257.
27. Fitzhugh D. J., Naik S., Gonzalez E., Caughman S. W. and Hwang S. T. (2000): CC chemokine receptor 6 (CCR6) is a marker for memory T cells that arrest on activated human dermal microvascular endothelium under shear stress. J. Invest. Dermatol., **115**, 332.
28. Fontenot J. D., Dooley J. L., Farr A. G. and Rudensky A. Y. (2005): Developmental regulation of Foxp3 expression during ontogeny. J. Exp. Med., **202**, 901–906.
29. Fontenot J. D., Gavin M. A. and Rudensky A. Y. (2003): Foxp3 programs the development and function of CD4+CD25+ regulatory T cells. Nat. Immunol., **4**, 330–336.
30. Fontenot J. D., Rasmussen J. P., Williams L. M., Dooley J. L., Farr A. G. and Rudensky A. Y. (2005): Regulatory T cell lineage specification by the forkhead transcription factor foxp3. Immunity, **22**, 329–341.
31. Forster R., Mattis A. E., Kremmer E., Wolf E., Brem G. and Lipp M. (1996): A putative chemokine receptor, BLR1, directs B cell migration to defined lymphoid organs and specific anatomic compartments of the spleen. Cell, **87**, 1037–1047.
32. Forster R., Schubel A., Breitfeld D., Kremmer E., Renner--Muller I., Wolf E. and Lipp M. (1999): CCR7 coordinates the primary immune response by establishing functional microenvironments in secondary lymphoid organs. Cell, **99**, 23–33.
33. Freeman C. M., Chiu B. C., Stolberg V. R., Hu J., Zeibecoglou K., Lukacs N. W., Lira S. A., Kunkel S. L. and Chensue S. W. (2005): CCR8 is expressed by antigen-elicited, IL-10-producing CD4+CD25+ T cells, which regulate Th2-mediated granuloma formation in mice. J. Immunol., **174**, 1962–1970.
34. Fu S., Yopp A. C., Mao X., Chen D., Zhang N., Mao M., Ding Y. and Bromberg J. S. (2004): CD4+ CD25+ CD62+ T-regulatory cell subset has optimal suppressive and proliferative potential. Am. J. Transplant., **4**, 65–78.
35. Gondek D. C., Lu L. F., Quezada S. A., Sakaguchi S. and Noelle R. J. (2005): Cutting edge: contact-mediated suppression by CD4+CD25+ regulatory cells involves a

granzyme B-dependent, perforin-independent mechanism. J. Immunol., **174**, 1783–1786.
36. Greaves D. R., Wang W., Dairaghi D. J., Dieu M. C., Saint--Vis B., Franz-Bacon K., Rossi D., Caux C., McClanahan T., Gordon S., Zlotnik A. and Schall T. J. (1997): CCR6, a CC chemokine receptor that interacts with macrophage inflammatory protein 3alpha and is highly expressed in human dendritic cells. J. Exp. Med., **186**, 837–844.
37. Grohmann U., Orabona C., Fallarino F., Vacca C., Calcinaro F., Falorni A., Candeloro P., Belladonna M. L., Bianchi R., Fioretti M. C. and Puccetti P. (2002): CTLA-4--Ig regulates tryptophan catabolism *in vivo*. Nat. Immunol., **3**, 1097–1101.
38. Grossman W. J., Verbsky J. W., Barchet W., Colonna M., Atkinson J. P. and Ley T. J. (2004): Human T regulatory cells can use the perforin pathway to cause autologous target cell death. Immunity, **21**, 589–601.
39. Groux H., O'Garra A., Bigler M., Rouleau M., Antonenko S., de Vries J. E. and Roncarolo M. G. (1997): A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. Nature, **389**, 737–742.
40. Hamann A., Andrew D. P., Jablonski-Westrich D., Holzmann B. and Butcher E. C. (1994): Role of alpha 4-integrins in lymphocyte homing to mucosal tissues *in vivo*. J. Immunol., **152**, 3282–3293.
41. Hori S., Nomura T. and Sakaguchi S. (2003): Control of regulatory T cell development by the transcription factor Foxp3. Science, **299**, 1057–1061.
42. Huehn J., Siegmund K., Lehmann J. C., Siewert C., Haubold U., Feuerer M., Debes G. F., Lauber J., Frey O., Przybylski G. K., Niesner U., De La Rosa M., Schmidt C. A., Brauer R., Buer J., Scheffold A. and Hamann A. (2004): Developmental stage, phenotype, and migration distinguish naive- and effector/memory-like CD4+ regulatory T cells. J. Exp. Med., **199**, 303–313.
43. Iellem A., Colantonio L. and D'Ambrosio D. (2003): Skin--versus gut-skewed homing receptor expression and intrinsic CCR4 expression on human peripheral blood CD4+CD25+ suppressor T cells. Eur. J. Immunol., **33**, 1488–1496.
44. Iwata M., Hirakiyama A., Eshima Y., Kagechika H., Kato C. and Song S. Y. (2004): Retinoic acid imprints gut-homing specificity on T cells. Immunity, **21**, 527–538.
45. Johansson-Lindbom B., Svensson M., Wurbel M. A., Malissen B., Marquez G. and Agace W. (2003): Selective generation of gut tropic T cells in gut-associated lymphoid tissue (GALT): requirement for GALT dendritic cells and adjuvant. J. Exp. Med., **198**, 963–969.
46. Johnston B. and Butcher E. C. (2002): Chemokines in rapid leukocyte adhesion triggering and migration. Semin. Immunol., **14**, 83–92.
47. Jordan M. S., Boesteanu A., Reed A. J., Petrone A. L., Holenbeck A. E., Lerman M. A., Naji A. and Caton A. J. (2001): Thymic selection of CD4+CD25+ regulatory T cells induced by an agonist self-peptide. Nat. Immunol., **2**, 301–306.
48. Kang S. G., Piniecki R. J., Hogenesch H., Lim H. W., Wiebke E., Braun S. E., Matsumoto S. and Kim C. H. (2007): Identification of a chemokine network that recruits FoxP3(+) regulatory T cells into chronically inflamed intestine. Gastroenterology, **132**, 966–981.
49. Khattri R., Cox T., Yasayko S. A. and Ramsdell F. (2003): An essential role for Scurfin in CD4+CD25+ T regulatory cells. Nat. Immunol., **4**, 337–342.
50. Kim C. H. (2005): The greater chemotactic network for lymphocyte trafficking: chemokines and beyond. Curr. Opin. Hematol., **12**, 298–304.
51. Kim C. H. (2006): Regulation of humoral immunity by FoxP3+ regulatory T cells. Expert Rev. Clin. Immunol., **2**, 859–868
52. Kim C. H. and Broxmeyer H. E. (1999): Chemokines: signal lamps for trafficking of T and B cells for development and effector function. J. Leukoc. Biol., **65**, 6–15.
53. Kim C. H., Campbell D. J. and Butcher E. C. (2001): Non--polarized memory T cells. Trends Immunol., **22**, 527–530.
54. Kim C. H., Nagata K. and Butcher E. C. (2003): Dendricitic cells support sequential reprogramming of chemoattractant profile during naive to effector T cells differentiation. J. Immunol., **171**, 152–158.
55. Kim C. H., Pelus L. M., White J. R. and Broxmeyer H. E. (1998): Differential chemotactic behavior of developing T cells in response to thymic chemokines. Blood, **91**, 4434–4443.
56. Kim C. H., Rott L., Kunkel E. J., Genovese M. C., Andrew D. P., Wu L. and Butcher E. C. (2001): Rules of chemokine receptor association with T cell polarization *in vivo*. J. Clin. Invest., **108**, 1331–1339.
57. Kim C. H., Rott L. S., Clark-Lewis I., Campbell D. J., Wu L. and Butcher E. C. (2001): Subspecialization of CXCR5+ T cells: B helper activity is focused in a germinal center-localized subset of CXCR5+ T cells. J. Exp. Med., **193**, 1373–1381.
58. Kim J. R., Lim H. W., Kang S. G., Hillsamer P. and Kim C. H. (2005): Human CD57+ germinal center-T cells are the major helpers for GC-B cells and induce class switch recombination. BMC Immunol., **6**, 3.
59. Kleinewietfeld M., Puentes F., Borsellino G., Battistini L., Rotzschke O. and Falk K. (2005): CCR6 expression defines regulatory effector/memory-like cells within the CD25(+)CD4+ T-cell subset. Blood, **105**, 2877–2886.
60. Kretschmer K., Apostolou I., Hawiger D., Khazaie K., Nussenzweig M. C. and von Boehmer H. (2005): Inducing and expanding regulatory T cell populations by foreign antigen. Nat. Immunol., **6**, 1219–1227.
61. Kunkel E. J., Campbell D. J. and Butcher E. C. (2003): Chemokines in lymphocyte trafficking and intestinal immunity. Microcirculation, **10**, 313–323.
62. Kunkel E. J., Campbell J. J., Haraldsen G., Pan J., Boisvert J., Roberts A. I., Ebert E. C., Vierra M. A., Goodman S. B., Genovese M. C., Wardlaw A. J., Greenberg H. B., Parker C. M., Butcher E. C., Andrew D. P. and Agace W. W. (2000): Lymphocyte CC chemokine receptor 9 and epithelial thymus-expressed chemokine (TECK) expression distinguish the small intestinal immune compartment: Epithelial expression of tissue-specific chemokines as an organizing principle in regional immunity. J. Exp. Med., **192**, 761–768.
63. Kunkel E. J., Kim C. H., Lazarus N. H., Vierra M. A., Soler D., Bowman E. P. and Butcher E. C. (2003): CCR10 expression is a common feature of circulating and mucosal epithelial tissue IgA Ab-secreting cells. J. Clin. Invest., **111**, 1001–1010.
64. Lee I., Wang L., Wells A. D., Dorf M. E., Ozkaynak E. and Hancock W. W. (2005): Recruitment of Foxp3+ T regulatory cells mediating allograft tolerance depends on the CCR4 chemokine receptor. J. Exp. Med., **201**, 1037–1044.
65. Lee J., Kang S. G. and Kim C. H. (2007): FoxP3+ T cells undergo conventional first switch to lymphoid tissue hom-

ing receptors in thymus but accelerated second switch to non-lymphoid tissue homing receptors in secondary lymphoid tissues. J. Immunol., **178**, 301–311.
66. Li L. and Choi Y. S. (2002): Follicular dendritic cell-signaling molecules required for proliferation and differentiation of GC-B cells. Semin. Immunol., **14**, 259–266.
67. Lim H. W., Broxmeyer H. E. and Kim C. H. (2006): Regulation of trafficking receptor expression in human forkhead box P3+ regulatory T cells. J. Immunol., **177**, 840–851.
68. Lim H. W., Hillsamer P., Banham A. H. and Kim C. H. (2005): Cutting edge: Direct suppression of B cells by CD4+CD25+ regulatory T cells. J. Immunol., **175**, 4180–4183.
69. Lim H. W., Hillsamer P. and Kim C. H. (2004): Regulatory T cells can migrate to follicles upon T cell activation and suppress GC-Th cells and GC-Th cell-driven B cell responses. J. Clin. Invest., **114**, 1640–1649.
70. Loetscher P., Uguccioni M., Bordoli L., Baggiolini M., Moser B., Chizzolini C. and Dayer J. M. (1998): CCR5 is characteristic of Th1 lymphocytes. Nature, **391**, 344–345.
71. Lopes J. E., Torgerson T. R., Schubert L. A., Anover S. D., Ocheltree E. L., Ochs H. D. and Ziegler S. F. (2006): Analysis of FOXP3 reveals multiple domains required for its function as a transcriptional repressor. J. Immunol., **177**, 3133–3142.
72. Luo Y., Laning J., Devi S., Mak J., Schall T. J. and Dorf M. E. (1994): Biologic activities of the murine beta-chemokine TCA3. J. Immunol., **153**, 4616–4624.
73. Manavalan J. S., Kim-Schulze S., Scotto L., Naiyer A. J., Vlad G., Colombo P. C., Marboe C., Mancini D., Cortesini R. and Suciu-Foca N. (2004): Alloantigen specific CD8+CD28– FOXP3+ T suppressor cells induce ILT3+ ILT4+ tolerogenic endothelial cells, inhibiting alloreactivity. Int. Immunol., **16**, 1055–1068.
74. Mantel P. Y., Ouaked N., Ruckert B., Karagiannidis C., Welz R., Blaser K. and Schmidt-Weber C. B. (2006): Molecular mechanisms underlying FOXP3 induction in human T cells. J. Immunol., **176**, 3593–3602.
75. Manzotti C. N., Tipping H., Perry L. C., Mead K. I., Blair P. J., Zheng Y. and Sansom D. M. (2002): Inhibition of human T cell proliferation by CTLA-4 utilizes CD80 and requires CD25+ regulatory T cells. Eur. J. Immunol., **32**, 2888–2896.
76. McHeyzer-Williams L. J., Malherbe L. P. and McHeyzer--Williams M. G. (2006): Helper T cell-regulated B cell immunity. Curr. Top. Microbiol. Immunol., **311**, 59–83.
77. Mora J. R., Bono M. R., Manjunath N., Weninger W., Cavanagh L. L., Rosemblatt, M. and Von Andrian U. H. (2003): Selective imprinting of gut-homing T cells by Peyer's patch dendritic cells. Nature, **424**, 88–93.
78. Mqadmi A., Zheng X. and Yazdanbakhsh K. (2005): CD4+CD25+ regulatory T cells control induction of autoimmune hemolytic anemia. Blood, **105**, 3746–3748.
79. Nakamura K., Kitani A. and Strober W. (2001): Cell contact-dependent immunosuppression by CD4(+)CD25(+) regulatory T cells is mediated by cell surface-bound transforming growth factor beta. J. Exp. Med., **194**, 629–644.
80. Otterbein L. E., Soares M. P., Yamashita K. and Bach F. H. (2003): Heme oxygenase-1: unleashing the protective properties of heme. Trends Immunol., **24**, 449–455.
81. Pae H. O., Oh G. S., Choi B. M., Chae S. C., Kim Y. M., Chung K. R. and Chung H. T. (2004): Carbon monoxide produced by heme oxygenase-1 suppresses T cell proliferation via inhibition of IL-2 production. J. Immunol., **172**, 4744–4751.
82. Pan J., Kunkel E. J., Gosslar U., Lazarus N., Langdon P., Broadwell K., Vierra M. A., Genovese M. C., Butcher E. C. and Soler D. (2000): A novel chemokine ligand for CCR10 and CCR3 expressed by epithelial cells in mucosal tissues. J. Immunol., **165**, 2943–2949.
83. Patel D. D. (2001): Escape from tolerance in the human X-linked autoimmunity-allergic disregulation syndrome and the Scurfy mouse. J. Clin. Invest., **107**, 155–157.
84. Piccirillo C. A. and Shevach E. M. (2001): Cutting edge: control of CD8+ T cell activation by CD4+CD25+ immunoregulatory cells. J. Immunol., **167**, 1137–1140.
85. Prockop S. and Petrie H. T. (2000): Cell migration and the anatomic control of thymocyte precursor differentiation. Semin. Immunol., **12**, 435–444.
86. Roncador G., Brown P. J., Maestre L., Hue S., Martinez-Torrecuadrada J. L., Ling K. L., Pratap S., Toms C., Fox B. C., Cerundolo V., Powrie F. and Banham A. H. (2005): Analysis of FOXP3 protein expression in human CD4(+)CD25(+) regulatory T cells at the single-cell level. Eur. J. Immunol., **35**, 1681–1691.
87. Roos R. S., Loetscher M., Legler D. F., Clark-Lewis I., Baggiolini M. and Moser B. (1997): Identification of CCR8, the receptor for the human CC chemokine I-309. J. Biol. Chem., **272**, 17251–17254.
88. Rouse B. T., Sarangi P. P. and Suvas S. (2006): Regulatory T cells in virus infections. Immunol. Rev., **212**, 272–286.
89. Sakaguchi S. (2005): Naturally arising Foxp3-expressing CD25+CD4+ regulatory T cells in immunological tolerance to self and non-self. Nat. Immunol., **6**, 345–352.
90. Sakaguchi S., Sakaguchi N., Asano M., Itoh M. and Toda M. (1995): Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. J. Immunol., **155**, 1151–1164.
91. Sallusto F., Lenig D., Mackay C. R. and Lanzavecchia A. (1998): Flexible programs of chemokine receptor expression on human polarized T helper 1 and 2 lymphocytes. J. Exp. Med., **187**, 875–883.
92. Sato K., Balla J., Otterbein L., Smith R. N., Brouard S., Lin Y., Csizmadia E., Sevigny J., Robson S. C., Vercellotti G., Choi A. M., Bach F. H. and Soares M. P. (2001): Carbon monoxide generated by heme oxygenase-1 suppresses the rejection of mouse-to-rat cardiac transplants. J. Immunol., **166**, 4185–4194.
93. Sauty A., Dziejman M., Taha R. A., Iarossi A. S., Neote K., Garcia-Zepeda E. A., Hamid Q. and Luster A. D. (1999): The T cell-specific CXC chemokines IP-10, Mig, and I-TAC are expressed by activated human bronchial epithelial cells. J. Immunol., **162**, 3549–3558.
94. Schubert L. A., Jeffery E., Zhang Y., Ramsdell F. and Ziegler S. F. (2001): Scurfin (FOXP3) acts as a repressor of transcription and regulates T cell activation. J. Biol. Chem., **276**, 37672–37679.
95. Sekiya T., Miyamasu M., Imanishi M., Yamada H., Nakajima T., Yamaguchi M., Fujisawa T., Pawankar R., Sano Y., Ohta K., Ishii A., Morita Y., Yamamoto K., Matsushima K., Yoshie O. and Hirai K. (2000): Inducible expression of a Th2-type CC chemokine thymus- and activation-regulated chemokine by human bronchial epithelial cells. J. Immunol., **165**, 2205–2213.

96. Smyth M. J., Teng M. W., Swann J., Kyparissoudis K., Godfrey D. I. and Hayakawa Y. (2006): CD4+CD25+ T regulatory cells suppress NK cell-mediated immunotherapy of cancer. J. Immunol., **176**, 1582–1587.
97. Starr T. K., Jameson S. C. and Hogquist K. A. (2003): Positive and negative selection of T cells. Annu. Rev. Immunol., **21**, 139–176.
98. Stein J. V., Rot A., Luo Y., Narasimhaswamy M., Nakano H., Gunn M. D., Matsuzawa A., Quackenbush E. J., Dorf M. E. and von Andrian U. H. (2000): The CC chemokine thymus-derived chemotactic agent 4 (TCA-4, secondary lymphoid tissue chemokine, 6Ckine, exodus-2) triggers lymphocyte function-associated antigen 1-mediated arrest of rolling T lymphocytes in peripheral lymph node high endothelial venules. J. Exp. Med., **191**, 61–76.
99. Szanya V., Ermann J., Taylor C., Holness C. and Fathman C. G. (2002): The subpopulation of CD4+CD25+ splenocytes that delays adoptive transfer of diabetes expresses L-selectin and high levels of CCR7. J. Immunol., **169**, 2461–2465.
100. Taams L. S., van Amelsfort J. M., Tiemessen M. M., Jacobs K. M., de Jong E. C., Akbar A. N., Bijlsma J. W. and Lafeber F. P. (2005): Modulation of monocyte/ macrophage function by human CD4+CD25+ regulatory T cells. Hum. Immunol., **66**, 222–230.
101. Taylor P. A., Panoskaltsis-Mortari A., Swedin J. M., Lucas P. J., Gress R. E., Levine B. L., June C. H., Serody J. S. and Blazar B. R. (2004): L-Selectin(hi) but not the L-selectin(lo) CD4+25+ T-regulatory cells are potent inhibitors of GVHD and BM graft rejection. Blood, **104**, 3804–3812.
102. Thornton A. M. and Shevach E. M. (1998): CD4+CD25+ immunoregulatory T cells suppress polyclonal T cell activation *in vitro* by inhibiting interleukin 2 production. J. Exp. Med., **188**, 287–296.
103. Tiffany H. L., Lautens L. L., Gao J. L., Pease J., Locati M., Combadiere C., Modi W., Bonner T. I. and Murphy P. M. (1997): Identification of CCR8: a human monocyte and thymus receptor for the CC chemokine I-309. J. Exp. Med., **186**, 165–170.
104. van Nierop K. and de Groot C. (2002): Human follicular dendritic cells: function, origin and development. Semin.Immunol., **14**, 251–257.
105. Venturi G. M., Conway R. M., Steeber D. A. and Tedder T. F. (2007): CD25+CD4+ regulatory T cell migration requires L-selectin expression: L-selectin transcriptional regulation balances constitutive receptor turnover. J. Immunol., **178**, 291–300.
106. von Boehmer H. (2005): Mechanisms of suppression by suppressor T cells. Nat. Immunol., **6**, 338–344.
107. Walker M. R., Kasprowicz D. J., Gersuk V. H., Benard A., Van Landeghen M., Buckner J. H. and Ziegler S. F. (2003): Induction of FoxP3 and acquisition of T regulatory activity by stimulated human CD4+CD25– T cells. J. Clin. Invest., **112**, 1437–1443.
108. Wan Y. Y. and Flavell R. A. (2005): Identifying Foxp3-expressing suppressor T cells with a bicistronic reporter. Proc. Natl. Acad. Sci. USA, **102**, 5126–5131.
109. Warnock R. A., Campbell J. J., Dorf M. E., Matsuzawa A., McEvoy L. M.and Butcher E. C. (2000): The role of chemokines in the microenvironmental control of T versus B cell arrest in Peyer's patch high endothelial venules. J. Exp. Med., **191**, 77–88.
110. Wildin R. S., Ramsdell F., Peake J., Faravelli F., Casanova J. L., Buist N., Levy-Lahad E., Mazzella M., Goulet O., Perroni L., Bricarelli F. D., Byrne G., McEuen M., Proll S., Appleby M. and Brunkow M. E. (2001): X-linked neonatal diabetes mellitus, enteropathy and endocrinopathy syndrome is the human equivalent of mouse scurfy. Nat. Genet., **27**, 18–20.
111. Williams I. R. (2006): CCR6 and CCL20: partners in intestinal immunity and lymphorganogenesis. Ann. NY Acad. Sci., **1072**, 52–61.
112. Wilson S. D., Kuchroo V. K., Israel D. I. and Dorf M. E. (1990): Expression and characterization of TCA3: a murine inflammatory protein. J. Immunol., **145**, 2745–2750.
113. Wood K. J. and Sakaguchi S. (2003): Regulatory T cells in transplantation tolerance. Nat. Rev. Immunol., **3**, 199–210.
114. Wu Y., Borde M., Heissmeyer V., Feuerer M., Lapan A. D., Stroud J. C., Bates D. L., Guo L., Han A., Ziegler S. F., Mathis D., Benoist C., Chen L. and Rao A., (2006): FOXP3 controls regulatory T cell function through cooperation with NFAT. Cell, **126**, 375–387.
115. Wysocki C. A., Jiang Q., Panoskaltsis-Mortari A., Taylor P. A., McKinnon K. P., Su L., Blazar B. R. and Serody J. S. (2005): Critical role for CCR5 in the function of donor CD4+CD25+ regulatory T cells during acute graft-versus-host disease. Blood, **106**, 3300–3307.
116. Youn B. S., Kim C. H., Smith F. O. and Broxmeyer H. E. (1999): TECK, an efficacious chemoattractant for human thymocytes, uses GPR-9-6/CCR9 as a specific receptor. Blood, **94**, 2533–2536.
117. Zaballos A., Gutierrez J., Varona R., Ardavin C. and Marquez G. (1999): Cutting edge: identification of the orphan chemokine receptor GPR-9-6 as CCR9, the receptor for the chemokine TECK. J. Immunol., **162**, 5671–5675.
118. Zabel B. A., Agace W. W., Campbell J. J., Heath H. M., Parent D., Roberts A. I., Ebert E. C., Kassam N., Qin S., Zovko M., LaRosa G. J., Yang L. L., Soler D., Butcher E. C., Ponath P. D., Parker C. M. and Andrew D. P. (1999): Human G protein-coupled receptor GPR-9-6/CC chemokine receptor 9 is selectively expressed on intestinal homing T lymphocytes, mucosal lymphocytes, and thymocytes and is required for thymus-expressed chemokine--mediated chemotaxis. J. Exp. Med., **190**, 1241–1256.
119. Zhang X., Koldzic D. N., Izikson L., Reddy J., Nazareno R. F., Sakaguchi S., Kuchroo V. K. and Weiner H. L. (2004): IL-10 is involved in the suppression of experimental autoimmune encephalomyelitis by CD25+CD4+ regulatory T cells. Int. Immunol., **16**, 249–256.
120. Zhao D. M., Thornton A. M., DiPaolo R. J. and Shevach E. M. (2006): Activated CD4+CD25+ T cells selectively kill B lymphocytes. Blood, **107**, 3925–3932.
121. Zheng S. G., Gray J. D., Ohtsuka K., Yamagiwa S. and Horwitz D. A. (2002): Generation *ex vivo* of TGF-beta--producing regulatory T cells from CD4+CD25- precursors. J. Immunol., **169**, 4183–4189.
122. Ziegler S. F. (2006): FOXP3: of mice and men. Annu. Rev. Immunol., **24**, 209–226.
123. Zingoni A., Soto H., Hedrick J. A., Stoppacciaro A., Storlazzi C. T., Sinigaglia F., D'Ambrosio D., O'Garra A., Robinson D., Rocchi M., Santoni A., Zlotnik A. and Napolitano M. (1998): The chemokine receptor CCR8 is preferentially expressed in Th2 but not Th1 cells. J. Immunol., **161**, 547–551.