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Regulatory T-cell Trafficking: From Thymic Development to Tumor-Induced Immune Suppression

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Abstract

Regulatory T cells (Tregs) have become a priority for many investigators in immunology due to their potent immunosuppressive and tolerogenic effects. While Treg activity is required for normal immune homeostasis, dysregulation of their numbers can induce autoimmunity or aid in the pathogenesis of disease. Therefore, great effort has been made to understand the mechanisms by which Tregs accumulate in different areas of the body. Like other lymphocytes, Tregs migrate in response to a network of chemotactic stimuli involving chemokines, chemokine receptors, integrins, and their corresponding ligands. However, many of these stimuli are exclusive to Tregs, inducing their migration while leaving conventional populations unaffected. It is these selective stimuli that result in increased ratios of Tregs among conventional effector populations, leading to changes in immune suppression and homeostasis. This review explores selective Treg trafficking during thymic Treg development, migration to secondary lymphoid tissues and emigration into the periphery during homeostatic conditions, inflammation, and the tumor microenvironment, placing emphasis on stimuli that selectively recruits Tregs to target locations.

Keywords

regulatory T cell; Treg; migration; trafficking; localization; chemokine; inflammation; cancer; immune suppression

I. Introduction

T cells harboring the ability to suppress the immune response are integral components in immunity. Modern immunologists now recognize the critical role that these regulatory T cells (Tregs) play in preserving immune homeostasis.^{1,2} However, dysregulation of Treg numbers leads to the pathogenesis of autoimmune disorders³⁻⁸ and can contribute to tumor-induced immune suppression.⁹ The suppressive capacity of any particular Treg population is not governed by their numbers alone, but rather by the ratio of Tregs to conventional effector cells,¹⁰ with higher ratios resulting in immune suppression¹⁰ and lower ratios

resulting in autoimmunity^{3, 6} or graft rejection.¹¹ It is therefore critical to understand how Tregs traffic and accumulate at different sites within the body, and how changes in these migratory pathways can lead to deviation from immune homeostasis and contribute to the pathogenesis of disease.

Like all leukocytes, Tregs traffic to different parts of the body at different stages of development, maturation, and activation. The trafficking of T cells is mediated by a network of cytokines, integrins, chemokines, and matching receptors. Chemokines are divided into the CXC group and the CC group, so named for the patterns of cystine residues in their binding domains. In general, both CC and CXC chemokines exhibit basal affinity for a wide range of chemokine receptors, but only display high affinity for a select few.¹²⁻¹⁶ Therefore, while T cells display chemotactic responses to various chemokines from both groups, a few specific chemokines can elicit preferential chemotaxis for subpopulations expressing the appropriate high-affinity receptors. It is these selective pathways that can lead to increased ratios of a particular subpopulation of cells. For Tregs, selective recruitment and altered frequencies can lead to changes in immune homeostasis. This review will evaluate Treg trafficking in both normal homeostatic conditions and in disease states, focusing on stimuli that selectively recruit Tregs over conventional effector populations (Table 1).

Many types of Tregs have been described, and semantics has further confounded Treg nomenclature. The most basic type are the naturally occurring Tregs (nTregs). These cells undergo maturation in the thymus in a manner similar to that of conventional T cells,¹⁷ but are selected for based on high affinity for self-antigens presented by thymic epithelial cells.¹⁸⁻²⁰ These nTregs then emigrate from the thymus into the periphery and secondary lymph tissues,²¹ where they exist at baseline levels throughout the body. In the periphery, nTregs make up 6% to 10% of all CD4⁺ (cellular determinant 4-positive) T cells in humans and in mice,²²⁻²⁵ although the bone marrow contains higher baseline levels in both species.²⁵ Expression of the transcription factor FoxP3 (Forkhead box protein 3) appears fairly restricted to nTregs, making it the most widely utilized marker to identify these cells.^{1, 2} However, exceptions exist: in humans, FoxP3 expression has been reported in other subpopulations of suppressive T cells²⁶⁻²⁸ and transiently in some conventional T cells during activation.²⁹⁻³¹ In the periphery or secondary lymph tissue, nTregs can be activated when they encounter specific self-antigen presented in the context of the major histocompatibility complex,³² but exude non-specific suppression on effector T cells,³³ antigen-presenting cells,³⁴ natural killer (NK) cells,³⁵ and B cells.³⁶

In contrast to nTregs, other suppressive T-cell populations can be induced in the periphery by a wide array of inflammatory mediators and/or tolerogenic T-cell receptor (TCR)-signaling events.³⁷ In humans, some inducible Treg populations can acquire FoxP3,²⁶⁻²⁸ but most do not. Inducible Tregs are associated with environmental queues, and are generally absent in the periphery under homeostatic conditions. Instead, inducible Tregs emerge from conventional effector populations in response to stimuli associated with a suppressive or otherwise altered microenvironment. When induced, these cells also traffic in response to network of migratory signals, although in many cases the specific factors and receptors involved may be distinct from those for nTregs.³⁸

II. Early Trafficking of Tregs in the Thymus

The majority of thymocytes expressing high-affinity TCRs to self-peptides are selectively destroyed in the thymus to prevent the development of self-reactive effector populations.³⁹ However, a select minority of highly self-reactive thymocytes averts negative selection, giving rise to FoxP3-expressing nTregs.¹⁸ Approximately 5% of CD4 single-positive thymocytes become FoxP3⁺ prior to emigration from the thymus. This is in contrast to CD8

single-positive thymocytes, which contain less than 1% FoxP3-expressing cells.⁴⁰ Escape from negative selection is limited to a minority of thymocytes residing among groups of epithelial cells within the medulla called the Hassel's corpuscles (HC), and it is here that FoxP3 expression is observed in developing thymocytes.⁴¹ Studies in double-transgenic mice reveal that only T cells with very high-affinity transgenic TCRs acquire FoxP3 expression in the thymus,^{18,42} and gene-expression studies indicate that FoxP3 expression is dependent upon thymic peptide presentation during positive selection.⁴⁰ Collectively, the HC appears to be a privileged area in which thymocytes commit to a Treg lineage during a unique positive and negative selection regime targeting high-affinity TCRs to self-peptides. T cells with such TCRs would be eliminated elsewhere in the medulla. Localization of developing Tregs to the HC is therefore critical to their survival.

Developing Treg recruitment and retention may be accomplished both directly and indirectly by epithelial cells within the HC. First, epithelial-derived factors such as the EBI1-ligand chemokine (CCL19) and the macrophage-derived chemokine (MDC/CCL22) are highly expressed in distinct subsets of the medulla such as the HC,⁴³ where high levels of Tregs congregate.⁴¹ Secondly, HC epithelial cells produce a cytokine milieu that is distinct from nominal thymic stroma,⁴³⁻⁴⁶ which greatly influences other resident cell populations. Notably, the production of thymic stromal lymphopoietin can activate dendritic cells in the HC and induce the production of the thymus and activation-regulated chemokine (TARC) and MDC.⁴¹ Both MDC and TARC have high affinity for CCR4 (CC chemokine receptor 4) and can induce selective chemoattraction of Tregs through this receptor.⁴⁷ High concentrations of CCR4⁺ thymocytes can be detected in the medulla, and in particular at the HC.⁴³ Interestingly, while CCR4 is expressed on developing thymic Tregs, its expression is not as prominent as CCR8,⁴⁸ which is primarily associated with the chemokine CCL1/I-309.⁴⁹ Indeed, recruitment of thymic Tregs to the medulla by both macrophage and epithelial cell-derived CCL1 has been demonstrated.⁴⁸ That same study also found CCL1 expression on epithelial cells lining the thymic septa, suggesting that the CCR8/CCL1 axis may not only play a role in recruiting Tregs to the medulla, but may also aid in their emigration from the thymus.

Another chemokine of interest in thymic Treg trafficking is SDF-1 (stromal-derived factor-1) due to its ability to induce potent chemoattractive responses in CXCR4⁺ (CXCR4 cytokine receptor) lymphocytes⁵⁰ and its unique expression in the HC.⁴⁶ However, CXCR4 expression is not limited to thymic Tregs and appears to mediate recruitment of CD4⁺CD8⁻ and CD4⁺CD8⁺ immature thymocytes in a broad manner.^{51,52} Thus, while SDF-1 may recruit early thymocytes to the HC, it alone may not be selective for Tregs. Given this broad association with early thymocytes, one could speculate that SDF-1 aids in the recruitment of pre-T lymphocytes to the HC, and that it is after the unique selection of high-affinity, self-reactive TCR clones that MDC, TARC, and CCL1 then serve to retain and traffic the newly developed Tregs within the HC. However, more comprehensive Treg-migration studies would be needed to validate such a linearity of trafficking signals within the thymus.

III. Migration of Tregs to Secondary Lymph Tissue

Polyclonal and highly reactive to self-peptides, naive nTregs emigrate from the thymus and traffic to secondary lymph tissues, where they can exert suppressive effects on conventional T and B cells⁵³ and mediate immune homeostasis. Chemotaxis studies demonstrate that naive nTregs migrate toward CCL19 in a CCR7-dependent manner, and that this migration results in Treg homing to the T-cell zones in lymph nodes.⁵³ In addition, CD62L blockade results in reduced Treg numbers in draining lymph nodes.⁵⁴ Mice lacking CD62L have a 90% reduction in Treg numbers in the lymph nodes, although not in the spleen.⁵⁵ In vivo, CD62L⁻ and CD62L⁺ Tregs display similar regulatory capacities^{56,57}; however, adoptive

transfer of only CD62L expressing Tregs confers protection from graft-versus-host disease. This suggests that Treg lymph-node localization is critical for the regulation of immune homeostasis. However because conventional T-cell lymphoid homing is also CCR7 and CD62L dependent, these chemotactic stimuli may not be unique to Tregs. In a different murine allograft model, in addition to CCR7 dependency, activated Tregs in the periphery trafficked to draining lymph nodes in a CCR2- and CCR5-dependent manner. However, because CCR2 and CCR5 gene expression was similar between Tregs and conventional CD4⁺ T cells, and because CCR2 and CCR5 involvement was not studied in conventional T-cell migration, it remains unclear whether CCR2 and CCR5 represent unique migratory signals for Treg lymph-node homing.⁵⁸ Interestingly, this same study indicated that CCR4 does not play a role in Treg trafficking to draining lymph nodes despite implicating its involvement in allograft homing.

Once at the T-cell zone, nTregs may become activated by presentation of self-antigen in the context of major histocompatibility complex via antigen-presenting cells.^{32,59} Upon activation, nTregs lose expression of CCR7 and in turn are no longer recruited or retained by CCL19. Concurrently, activated Tregs gain the expression of CXCR5 and are chemotactically responsive to CXCL13 (CXC chemokine ligand 13).⁵³ The CXCL13/CXCR5 axis is largely responsible for recruiting B cells to the B-cell zones in lymph nodes⁶⁰ and, with the exception of humeral-supporting T_H2 cells,⁶¹ is not typically associated with conventional T-cell recruitment. Thus, activated Tregs in the lymph nodes that gain CXCR5 expression are unique among T cells in that they localize to B-cell follicles. Here, activated Tregs can inhibit B-cell activation, expansion, and antibody production.⁵³ Because of this shift in B-/T-cell zone localization, newly activated Tregs are afforded the ability to suppress both T and B-cell-mediated immunity in response to a specific auto-antigen.

IV. Treg Migration to Peripheral Tissues

Mature Tregs migrate and take up residence in peripheral tissues, where they represent 6% to 10% of the CD4⁺ T-cell compartment.²²⁻²⁵ Because this frequency of Tregs is fairly consistent across peripheral organs and in the blood during nonpathological states, it is unclear whether unique stimuli exist for nominal Treg trafficking to different peripheral locations. The majority of studies regarding Treg migration to the periphery are in the context of inflammation, infection, or cancer (as discussed below). While these studies do not directly address normal Treg migration to the periphery, they do identify several chemokine axes that lead to increased Treg accumulation under specific pathological conditions. In this way, specific pathogens that induce Treg accumulation may avert or subdue beneficial immune responses.

One such example is paracoccidioidomycosis, a chronic infection largely afflicting rural Latin America and caused by the fungus *Paracoccidioides brasiliensis*. Typically infecting the lungs, this disease causes inflamed lesions with dense infiltrate consisting of neutrophils, macrophages, and both CD4⁺ and CD8⁺ effector T cells. Skin tests reveal adequate reactivity to fungal antigens,⁶² suggesting the ability to immunologically respond to the infection. However, altered cytokine expression in these lesions leads to key changes in chemokine production in the epithelium.⁶³ Particular attention should be paid to CCL4, which has high affinity for the receptor CCR5.⁶⁴ Increased CCL4 expression is correlated with increased CD4⁺CCR5⁺ Tregs within the fungal lesions.⁶⁵ In a mouse model of *P. brasiliensis* infection, Treg levels directly mediated the persistence of the infection, while mice deficient for CCR5 displayed reduced Treg migration to fungal lesions and increased dissemination of inflamed lesions.⁶⁶

Another pathogen that utilizes Treg accumulation is *Leishmania major*. Subcutaneous infection with this pathogen results in marked Treg accumulation and subsequent effector T-cell suppression.⁶⁷ The Tregs that accumulate at the sites of *L. major* infection appear to be a particular subset that expresses the α E integrin CD103.^{68,69} The major ligand for the α E β 7 integrin is E-cadherin,^{70,71} which is highly expressed in the dermal tissue surrounding *L. major* infection.⁷² Mice lacking CD103 display decreased Treg infiltration compared with wild-type controls, and appear to be resistant to *L. major* infection.⁷³ In addition to *L. major* infection, CD103 expression seems to define other subsets of inflammation-homing Tregs. These CD103⁺ Tregs have markedly reduced CD62L expression, while CD103⁻ Tregs are restricted to CCR7⁺ and CD62L⁺ populations localized in secondary lymph tissue.^{69,74,75}

Another study suggests that CD103 expression precedes Treg migration to inflamed tissue within the gut, and that CD103 expression is essential for the resolution of inflammation through Treg-mediated suppression of effector populations.⁷⁶ Interestingly, Treg homing to inflamed bowels is not only dependent on dendritic cells, but also on dendritic cell CD103 expression.⁷⁷ This dependency is somewhat puzzling, as CD103⁺ dendritic cells also localize to epithelia in the gut,⁷⁸ suggesting that CD103⁺ dendritic cells mediate Treg migration to the gut from within the target location. One explanation could lie in the propensity of dendritic cells to produce chemotactic factors themselves, in particular those associated with Treg recruitment. In this way, dendritic cells could attract Tregs through the production of chemokines in lieu of the target stroma. In support of this view, dendritic cells have the ability to produce CCL28,⁷⁹ which actively recruits CD103⁺ Tregs through CCR10 in inflamed human liver.⁸⁰ In the gut, CCR10 expression on immigrating Tregs does play a role in Treg recruitment.⁸¹ However, the likelihood of this mechanism mediating Treg recruitment to the inflamed gut is reduced by the fact that intestinal epithelium constitutively expresses high levels of CCL28.⁸² In comparison, the contribution of infiltrate-derived CCL28 is likely minimal. Further studies are needed to elucidate the relationship between CD103 expression on dendritic cells and CD103⁺ Treg homing to the inflamed gut.

While the Treg frequency among effector T cells is fairly constant across the majority of peripheral organs under normal conditions, the bone marrow constitutes a notable exception. Treg cells are highly elevated in the bone marrow of both mice and humans,²⁵ where they elicit suppressive effects on resident populations. The bone marrow has long been the obvious purveyor of hematopoiesis, but recent findings suggest that it may also play an active role in immunity by supporting the extended survival of plasma cells⁸³ and serving as a reservoir for effector memory T cells.^{84,85}

Homeostatic proliferation is the crucial process by which memory T cells persist without contact with antigen,^{86,87} and this process is dependent on interleukin (IL)-7 and IL-15. The bone marrow appears to harbor homeostatic proliferation to a greater extent than other organs or secondary lymph tissues.⁸⁴ These bone marrow-resident memory T cells are distinct from central memory T cells, which express CD62L and are localized to secondary lymph tissues.⁸⁸ Studies investigating memory T cells specific for tumor antigen have revealed that these cells are functional when removed from the bone marrow of tumor-bearing mice and humans and are able to mount a beneficial anti-tumor immune response.⁸⁹⁻⁹¹ However, the persistence of tumor growth in the host suggests that these memory cells are effectively suppressed in vivo, possibly due to the observed increases in baseline Treg levels inside the bone marrow.

Because of the above characteristics, there is great interest in exploring Treg recruitment to the bone marrow. Studies utilizing a bicistronic promoter that inserts a fluorescent promoter into the endogenous FoxP3 locus have been used to directly track Treg movement within mice.⁹² These studies reveal significant accumulation of CXCR4⁺ Tregs inside the bone

marrow. CXCR4 expression is up-regulated on Tregs following activation, at which time they become responsive to SDF-1 α and can migrate to the bone marrow in a SDF-1 α - and CXCR4-dependent manner. However, Treg accumulation in the bone marrow could be reversed by granulocyte colony-stimulating factor, which appears to down-regulate SDF-1 α expression in the bone marrow²⁵ and mobilize Tregs into the periphery. This study also showed that CCR4-associated chemokines are not expressed in significant quantities in either human or mouse bone marrow, suggesting that CCR4 may not play a significant role in selective Treg recruitment to the bone marrow, as it does elsewhere.

V. Treg Recruitment to the Tumor Microenvironment

At one time, tumors were thought to be irrelevant to the immune system, easily being dismissed as “self.” However, after the discovery of tumor antigens, tumors were found to be immunogenic,^{93,94} and the race to exploit this immunogenicity was on. Unfortunately, tumor immunogenicity is more complicated than was initially thought. Today, it is known that beneficial immunity against cancer is subdued through a process of tumor-induced immune suppression. This process involves many different facets, not the least of which involves the accumulation of suppressive cell types such as Tregs. Increased Treg frequencies in cancer are well documented, with elevated numbers being reported in the circulation and in the tissues of lung cancer,⁹⁵ breast cancer,⁹⁶ ovarian carcinoma,²² melanoma,⁹⁷⁻⁹⁹ liver cancer,^{100,101} gastric cancer,¹⁰² head and neck squamous cell carcinoma,^{103,104} and lymphoma,¹⁰⁵ among others. These elevated levels of Tregs are correlated with poor prognosis in many cancers,^{22,106-108} while their depletion may aid in the induction of an anti-tumor response.^{9,109,110} Not only do Tregs promote tumor-induced immune suppression and prevent natural tumor clearance, but they also hinder immunotherapeutic strategies designed to actively induce anti-tumor immunity.^{111,112} Recent efforts to understand Treg accumulation in the tumor microenvironment has greatly increased our knowledge of Treg tumor trafficking, and has revealed potential therapeutic targets with which to combat tumor-induced immune suppression.

The accumulation of Tregs at the tumor site is due in part to selective recruitment mediated by chemokines, and heightened expression of these chemokines is correlated with elevated Treg levels in many cancer types. By far, the most described axis in selective Treg recruitment to the tumor is through the CCR4 and the CCR4-associated chemokines CCL22 and CCL17. This recruitment pathway was first described in human ovarian cancer patients who displayed increased CCR4⁺ Tregs at the primary tumor site and decreased numbers in regional draining lymph nodes. The ovarian tumors themselves displaying increased CCL22 production, and the addition of neutralizing antibody against CCL22 greatly reduced the ability of malignant ascites to attract Tregs in an in vitro assay.²² While this study did not find significant amounts of CCL17 produced by ovarian carcinoma, both CCR4 associated chemokines have been implicated in selective Treg recruitment to other cancer types, including Hodgkin's lymphoma,¹¹³ non-Hodgkin's lymphoma metastasized to the meninges,¹¹⁴ gastric cancer,¹¹⁵ and esophageal squamous cell carcinoma.¹¹⁶

CCR4 has also been shown to mediate Treg recruitment to human breast cancer, although CCL22 and CCL17 mediation of this effect appears more complex than in other cancer types. In primary breast tumors, CCL22 but not CCL17 selectively recruits Tregs through CCR4 to lymphoid aggregates surrounding the tumor and not specifically to the tumor bed itself. It is the increased Treg levels in these aggregates that are correlated with a negative outcome, not the Treg levels in the tumor bed itself. Interestingly, Tregs within these lymphoid aggregates displayed a highly activated phenotype compared with those found in the tumor mass.¹¹⁶ Because these activated Tregs are closely associated with dendritic cells within these lymphoid aggregates,¹¹⁷ it is easy to hypothesize that tumor antigen

presentation at the tumor site itself aids in Treg persistence. In contrast to primary breast cancer, a mouse model of metastatic breast cancer in the lung selectively recruited Tregs through CCL17.¹¹⁸ In this model, the trafficking of Tregs to the lung preceded metastasis, despite the simultaneous recruitment of the metastatic cancer cells through CCR4.

In a mouse model utilizing Lewis lung carcinoma (LLC), CCL22 was again implicated in selective Treg recruitment. However, in this system CCL22 was not produced by LLC cells or by normal lung epithelial cells. Instead, secreted CCL22 was limited to infiltrating CD11b⁺ cells within the tumor-bearing tissue. Further investigation revealed that NK cells expressing low levels of CD11b are responsible for the majority of secreted CCL22 from LLC-bearing lungs, and that these cells secrete CCL22 upon activation.¹¹⁹ This is surprising, given the beneficial role that has been established for NK cells in anti-tumor immunity.¹²⁰ Depletion of NK cells in this tumor model actually resulted in *increased* CCL22 and Treg levels in LLC-bearing tissue. The new source of CCL22 in these depleted animals was attributed to a large amount of infiltrating CD11b⁺CD11c⁺ cells, most likely myeloid dendritic cells. These cells were not found in normal or LLC-bearing tissue with intact NK populations, and appeared to overcompensate for the loss of NK cells in the context of CCL22 secretion.¹²¹ These studies reiterate the CCR4 chemokine axis in selective Treg recruitment, but also highlight an interesting point: because infiltrating populations can contribute to Treg-recruiting factors, caution must be taken when making conclusions based on cell lines alone. Instead, effort should be made to consider all components of the microenvironment, from stroma to infiltrate, and how these constituents can interact with each other to affect chemokine secretion.

While chemokines seem to have high affinity for select receptor(s), they also have a lower basal affinity for a wider range of receptors and are therefore often described as “promiscuous.” One study exploring CCR4-mediated recruitment of Tregs to gliomas found that, despite high levels of intracellular CCL22, it is CCL2 and not CCL22 that is actually secreted by the glioma cells. Neutralizing antibodies against CCL2 and CCR4 reveal that it is through this chemokine that Tregs are selectively recruited to the tumor site.¹²² While CCL2 is not widely defined as a ligand for CCR4, many CC chemokines can elicit some signaling activity through this receptor.¹²

Aside from the CCR4 chemokine axis, a few other chemokines and receptors have been shown to selectively recruit Tregs to the tumor microenvironment. In a murine model of pancreatic adenocarcinoma, increased Treg levels were associated with Treg CCR5 expression and gene expression of the CCR5 ligands CCL3, CCL4, and CCL5. Small hairpin RNA transduction targeting CCL5 in the tumor cell line prior to inoculation into mice reduced intratumor Treg levels by half and delayed tumor growth. Similar beneficial effects were seen using a small-molecule inhibitor of CCR5.¹²³ Another chemokine shown to induce selective migration of Tregs is CCL20. This chemokine has high affinity for CCR6 and has displayed chemotactic activity for CCR6⁺ Tregs.¹²⁴ Interestingly, Epstein-Barr virus infection increased the production of CCL20 from Hodgkin's lymphoma and induced the selective migration of Tregs, while cancer cells from Epstein-Barr virus-negative Hodgkin's patients had only basal expression of CCL20. Because Epstein-Barr virus is such an important etiological factor in many Hodgkin's cases, CCL20 production and Treg recruitment may represent a novel therapeutic target for Epstein-Barr virus-positive patients.¹²⁵

VI. Closing Remarks

T cells with the ability to suppress immunity are vital to normal immune function, but can also contribute to a wide range of pathological conditions. Because the numbers of Tregs in

relation to conventional effector populations is so important, an understanding of the mechanisms that lead to the recruitment and accumulation of these cells throughout the body becomes paramount. Elucidating the chemotactic axes, integrins, and other signaling factors by which Tregs traffic has revealed an ever-growing list of migratory signals that can be specific to certain conditions, suggesting that Treg compartmentalization may result from site-specific stimuli. However, clear tendencies are emerging. The migratory stimuli of naive Tregs appear similar to those of naive conventional populations, while peripherally activated Treg localization favors stimuli associated with inflammatory sites. In cancer, CCR4 and CCR4-associated chemokines seem to dominate Treg recruitment. This mechanism is similar to developing Tregs in the thymus. The most exciting prospect of this research is the possibility of using such specific pathways to selectively target problematic populations of Tregs while leaving non-problematic populations intact. Such therapies may be able to address problems such as tumor-induced immune suppression without the threat of undesirable autoimmune side effects.

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Abbreviations

CD	cellular determinant
CCL	CC chemokine ligand
CCR	CC chemokine receptor
CXCR	CXC chemokine receptor
FoxP3	Forkhead box protein 3
HC	Hassal's corpuscles
IL	interleukin
LLC	Lewis lung carcinoma
MDC	macrophage-derived chemokine
NK	natural killer
nTreg	naturally occurring regulatory T cell
SDF-1α	stromal-derived factor 1 α
TARC	thymus and activation regulated chemokine
TCR	T-cell receptor
Treg	regulatory T cell

Table 1
Summary of Reviewed Selective Treg Recruitment Axes

Chemokine/Integrin	Receptor	Context	Species	Reference
CCL19, CCL22	CCR4	Thymus, HC	Human	41,43
CCL1	CCR8	Thymus, HC	Human	48
CCL19	CCR7	Secondary LN	Human	53
CD62L		Secondary LN	Mouse	54,55
	CCR2	Secondary LN	Mouse	58
	CCR5	Secondary LN	Mouse	58
CXCL13	CXCR5	B-cell Follicles	Human	53
CCL4	CCR5	<i>Paracoccidioides brasiliensis</i>	Human, mouse	64-66
α E (CD103)	E-cadherin	<i>Leishmania major</i>	Mouse	68,69,73
CCL28	CCR10	Liver	Human	80
CXCL12	CXCR4	Bone marrow	Mouse	92
CCL22	CCR4	Ovarian cancer	Human	22
CCL17, CCL22	CCR4	Hodgkin's lymphoma	Human	113
CCL17, CCL22	CCR4	Non-Hodgkin's lymphoma	Human	114
CCL17, CCL22	CCR4	Gastric cancer	Human	115
CCL17, CCL22	CCR4	Esophageal squamous cell carcinoma	Human	116
CCL22	CCR4	Breast cancer	Human	117
CCL17	CCR4	Breast cancer	Mouse	118
CCL22	CCR4	Lewis lung carcinoma	Mouse	119,121
CCL2	CCR4	Glioma	Human	122
CCL3, CCL4, CCL5	CCR5	Pancreatic adenocarcinoma	Mouse	123
CCL20	CCR6	Epstein-Barr virus + Hodgkin's lymphoma	Human	125