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Back to the Thymus: Peripheral T Cells Come Home

J. Scott Hale and **Pamela J. Fink**

Department of Immunology, University of Washington, Seattle, WA 98195

Abstract

The thymus has long been known as the generative organ for the T cell arm of the immune system. To perform this role, the thymus was thought to require protection from antigenic and cellular insult from the “outside world”, with the notable exception of the continual influx of progenitor cells required to initiate the complicated process of T cell differentiation. Overwhelming evidence that mature T cells can recirculate and persist in the thymus has required us to revamp this earlier view of the thymus as detached from outside influence. In this review, we consider the evidence for T cell recirculation into the thymus, discuss the likely means and location of mature T cell entry, and speculate on the potential consequences of such close apposition between differentiating thymocytes and mature recirculating lymphocytes.

Keywords

thymus; T cell recirculation; negative selection; positive selection

INTRODUCTION

Prior to focusing on the potential impact on the thymus of immigrating peripheral T cells, a discussion of the highly regulated development of T cells within the thymic stromal cell maze is in order. T cell differentiation in the thymus is a complex and tightly controlled process that begins with the immigration of bone marrow-derived progenitor cells, and ends with the generation of self-tolerant, lineage committed T cells capable of performing an array of immune functions upon recognition of antigen in the context of molecules encoded by self major histocompatibility (MHC) genes (reviewed in¹). The T cell precursors that first enter the thymus do not express the antigen recognition machinery, lacking both the coreceptors (CD4 and CD8) that focus T cell attention on MHC molecules and the T cell receptors for antigen recognition (TCR $\alpha\beta$ and TCR $\gamma\delta$). The genes encoding these highly diverse TCRs undergo a carefully programmed series of DNA rearrangements triggered within the thymus in a stepwise fashion, beginning in CD4[−]CD8[−] (double negative or DN) thymocytes (reviewed in²). For conventional TCR $\alpha\beta$ T cells that recognize peptide antigens presented by classical MHC molecules, commitment to the T cell lineage is sealed by rearrangement of the TCR β gene. The process of β selection tests the accuracy of this rearrangement event, and drives the proliferation and CD4 and CD8 coreceptor expression by those cells expressing a functional TCR β chain (defined as one that pairs with the product of the unrearranged pre-T α gene)³. The result is a large population of CD4⁺CD8⁺ (double positive or DP) thymocytes that initiate TCR α rearrangement. Accurate TCR α rearrangement along with successful TCR $\alpha\beta$ chain pairing and surface expression are required for positive selection, the second critical checkpoint for maturing T cells. Positive selection is driven by the successful, low affinity interaction

between the expressed TCR $\alpha\beta$ receptor on a DP thymocyte and self-peptide in the context of self-MHC^{3,4}. Positive selection rescues DP thymocytes from the alternative destiny of programmed cell “death by neglect”, and drives the accurate alignment between coreceptor expression and lineage commitment^{1,3,4}. This process results in a population of CD4⁺CD8⁻ (single positive or SP) thymocytes that can differentiate into helper T cells upon further recognition of peptide presented by MHC class II molecules, and CD4⁻CD8⁺ SP thymocytes that can differentiate into killer T cells upon encounter with antigen presenting cells whose MHC class I molecules carry the appropriate peptides. At the DP or SP stages, thymocytes are subjected to negative selection, the third checkpoint that regulates T cell development. During this process, central to the establishment of self-tolerance among developing T cells, TCR $\alpha\beta$ ⁺ thymocytes that react with inappropriately high avidity to self peptide/MHC complexes are deleted⁵⁻⁷. The 1% of thymocytes that successfully transit β selection, positive selection, and negative selection undergo additional maturation that promotes their regulated exit from the thymus. After further maturation in the lymphoid periphery, these recent thymic emigrants join the pool of mature peripheral T cells. The induction of self-tolerance among any remaining self-reactive T cells continues in the lymphoid periphery by several means, including through the activity of regulatory T cells (Tregs, reviewed in⁸). The population of mature peripheral T cells recirculates from blood to the lymph and back again, patrolling the spleen and lymph nodes for foreign invaders. Lymphocyte recirculation is a carefully controlled, multistep process, regulated by the expression on lymphocytes of homing receptors (including integrins and chemokine receptors) and by the expression or elaboration by stromal elements of addressins, the ligands for lymphocyte homing receptors (reviewed in⁹⁻¹¹).

As with most developmental systems, the close association between differentiating thymocytes and the stromal elements of the thymus itself is key to the regulation of these maturation events. The thymus can be loosely categorized into densely packed cortical (outer) and more sparsely populated medullary (inner) regions (Figure 1)¹². It is where these regions meet, the cortico-medullary junction, that the postcapillary venules lie¹³⁻¹⁶. There is a very close association between the thymic epithelium and these postcapillary venules¹⁷, which are the only vessels in the thymus large enough to allow cellular extravasation¹⁸, and are surrounded by a well-defined peri-vascular space. This space appears to serve as a transit pathway for both progenitor cell entry and emigration of mature thymocytes¹⁶. In addition, the thymus likely contains lymphatic vessels, and these may also serve as entry and exit routes for lymphocytes^{14,15}. The nonthymocyte elements of the thymus include cortical and medullary thymic epithelial cells, dendritic cells, macrophages, and a small number of B cells. Cortical thymic epithelial cells are the primary mediators of positive selection^{3,4}, although hematopoietic cells are known to positively select some populations of developing thymocytes¹⁹. Medullary thymic epithelial cells that are specialized to express tissue-specific antigens and dendritic cells mediate negative selection^{5,6}. The importance of thymic architecture to T cell maturation is underscored by the recent observation that developing T cells traverse distinct thymic zones during the course of their differentiation^{20,21}. Progenitor cells enter the thymus via the vessels at the cortico-medullary junction, and the immature DN thymocytes migrate to the outer cortex, over the course of approximately 2 weeks, differentiating along their journey. Their DP progeny then retrace this migration pattern, more rapidly and in retrograde fashion, traveling back to the inner cortex, and from there, into the medulla, where most SP thymocytes reside²¹. Thus, the various stages of T cell differentiation, including TCR β gene rearrangement, β selection and cell proliferation, dual coreceptor expression, TCR α gene rearrangement, positive selection, lineage commitment, downregulation of inappropriate coreceptor expression, and negative selection, all take place in separate thymic microenvironments, defined by distinct stromal elements (Figure 1). It appears that most mature thymocytes leave for the periphery from the cortico-medullary junction, although when this pathway is blocked, exit from the cortex may also be possible²².

MATURE LYMPHOCYTES CAN REENTER THE THYMUS

Recirculation of mature lymphocytes to the thymus was documented shortly after general acceptance of the notion that the thymus, despite the signs of intrathymic cellular death, was at least partly responsible for exporting immune cells to the lymphoid periphery. Cells labeled in vivo with ^3H -thymidine were isolated from the lymph nodes draining an allogeneic skin graft, injected into syngeneic recipients, and recovered, in small numbers, 1–3 days post transfer from the host thymus²³. Additional reports followed^{24,25}, although the failure to consistently document the ability of lymphocytes to home to and persist in the thymus proved confusing^{26,27}. The ability to track cells by their immune functions enabled the more consistent detection of often rare recirculating cells in the thymus. Mature lymphocyte immigration into the thymus has now been well documented in the mouse^{23,28–43}, the rat^{25,44–48}, and the pig⁴⁹.

Which mature recirculating cell types are allowed access to the thymus? In most systems, B cells do not appear to enter the healthy adult thymus or persist there^{39,46}, but there are reports to the contrary, in both healthy^{30,47} and autoimmune individuals^{32,50}. Bone marrow-derived dendritic cells and other antigen presenting cells can travel to the thymus of allogeneic and syngeneic recipients under some conditions^{38,47,48,51,52}, but not others^{39,48,53}.

Much evidence suggests that the thymus lobes of healthy individuals are perhaps uniquely accessible to recirculating T cells. The T cell identity of at least some recirculating lymphocytes recovered from the thymus became clear from experiments in which T cell lines, induced in vivo⁴⁴ or in vitro⁴⁵, homed (albeit inefficiently) to the thymus. In the latter case, these thymic immigrants were recovered up to several months later as immunocompetent T cells. A few years after this report, Thy-1 allotype marked lymph node cells were transferred to congenic hosts that were then primed to minor histocompatibility antigens to induce a killer T cell response. Thy-1 typing of the resulting cytolytic effector cells revealed that 5–60% of the resulting cytolytic activity recovered from the host thymus was mediated by donor cells²⁸. The rule dictating the unidirectional traffic of mature T cells out of (but not into) the thymus clearly required rewriting.

Further technological advances have improved our ability to detect and quantify the contribution of recirculating T cells to the thymocyte pool. Whole body immunohistochemistry of adult recipients of allotype marked TCR $\alpha\beta$ transgenic T cells primed to their cognate antigen in the host environment revealed the entry into the host thymus of donor T cells⁵⁷. While the number of immigrant mature T cells peaked at approximately 10^6 per thymus, their numbers stabilized at 10^5 /thymus for up to 60 days post transfer and priming. Entry of mature cells into the thymus is not an indirect result of associated in vitro manipulations of the donor cells, as delivery of donor cells through parabiosis has also demonstrated immigration of T cells from one partner into the thymic lobes of the second parabiont^{31,41}. T cells do not reenter the thymus purely as a result of surgical perturbations or from the intravenous injection of a bolus of mature T cells. Recirculation of mature T cells to the thymus has also been demonstrated in unmanipulated mice in a genetically engineered model system. In mice transgenic for green fluorescent protein (GFP) under the control of the RAG2 promoter, developing thymocytes after the late DN stage fluoresce, as do mature SP thymocytes⁵⁴. Analysis of GFP⁺ mature T cells within the thymic lobes of such RAG2p-GFP transgenic mice has permitted the quantification of recirculating, nonfluorescent T cells in unmanipulated mice from 2 days to nearly 2 years of age^{40,42,54,55}. Work by Hale and colleagues revealed that the proportion of the SP compartment that is comprised of GFP⁺, recirculating, mature (CD24^{low}Qa2^{hi}) cells increases with age (particularly within the first five months), although in the steadily shrinking thymic lobes, the numbers of immigrants remain somewhat more constant (Figure 2).

WHAT TYPES OF MATURE T CELLS REENTER THE THYMUS?

Both CD4 and CD8 T cells appear to reenter the thymus^{29,33,40,42,54,56} in approximately the proportions they represent in secondary lymphoid organs and blood. Much has been written on the relative homing into the thymus of activated versus naive recirculating T cells. It is clear from experiments directly comparing the immigration of activated and naive T cells that prior exposure to antigen or mitogen enhances the homing of mature T cells to the thymus. Injection of alloantigen-activated blasts or naive T cells into Thy-1 allotypic hosts revealed an estimated 50-fold preference for thymic homing of the activated T cell population³³. T cells activated by antigen, either *in vivo*^{37,38,48} or *in vitro*⁴⁵, showed a similar pattern of thymic homing. Comparable results were obtained following injection of T cells sorted by phenotypic marker expression into naive and previously activated populations^{46,47}, although the fold preference of homing by previously activated cells in these experiments was a more modest 4–6 fold. Analysis of recirculating mature T cells in the thymic lobes of unmanipulated mice (Figure 2) also demonstrated that most cells are CD44^{hi}, and therefore previously activated⁴⁰. Reentry into the thymus may be particularly robust by T cells that have entered the S phase of the cell cycle³³, although it is clear that resting, previously activated cells also enter the thymus more efficiently than do naive cells^{46,47}.

While there is general agreement regarding the preferential thymic reentry of activated relative to naive T cells, it is likely this preference is a quantitative one. Thus, many reports have demonstrated that small numbers of naive, nonactivated T cells can also gain access to the thymus^{24,25,29,36,40,46,47}. In RAG2p-GFP transgenic mice, reentering GFP⁺ mature T cells are predominantly, but not exclusively, CD44^{hi}. Thus, 5–15% of GFP⁺ thymocytes are CD44^{low}, and therefore naive (Figure 2 and data not shown). Hale and coworkers found that approximately 600 recirculating T cells seeded the thymus of young adult recipients 4 days following injection of 6×10^6 naive, allotype marked T cells⁴⁰. Given the estimated 10% take of intravenously injected spleen and lymph node cells⁵⁷ (a number that agrees well with the number of donor cells recovered from the spleens of these recipients), an estimated 0.1% of naive T cells reenter the thymus and persist there⁴⁰. In contrast, injection of 10^7 alloantigen-activated T cell blasts resulted in 5×10^4 cells donor cells in the host thymus by day 6. Assuming a 10% take and no proliferation (an assumption that is very likely wrong), this translates to 5% of activated T cells that reenter the thymus³³.

WHERE AND HOW DO MATURE T CELLS REENTER THE THYMUS?

There appears to be general agreement that recirculating T cells enter the thymus through the postcapillary venules at the cortico-medullary junction^{13–16} and persist in the medulla^{29–31,33,37,47,56}. There are reports of recirculating cells in the cortex²³, although in these earlier experiments, a clear distinction between mature T cells and progenitor cells (known to take up residence in the cortex) could not be established. In more recent experiments, unambiguously mature T cells made a rare appearance in the cortex, at a frequency of 5-fold⁵⁶ or 20–60 fold lower than in the medulla, in which 0.2 to 0.3% of the cells were calculated to be of donor recirculating T cell origin²⁹.

A few groups have investigated the molecules that promote mature T cell immigration into the thymus. Migration into the thymus of previously activated peripheral T cells in the rat was found to be $\alpha 4$ integrin dependent. Entry into the thymus was blocked by antibody against VCAM-1, implicating the interaction between $\alpha 4$ integrin expressed on the T cell surface (probably paired with $\beta 1$) and VCAM-1 expressed on the thymic vasculature in T cell migration across the thymic endothelium and into the medullary compartment of the thymus⁴⁶. In the hyperplastic mouse thymus, expression on the T cell of L-selectin and $\alpha 4\beta 7$ integrin mediates the respective interaction between PNAd and MAdCAM-1 on the thymic vasculature or

stromal cells⁵⁸, thereby promoting T cell immigration^{59,60}. Whether T cell recirculation to the normal thymus is similarly controlled is unclear, although L-selectin expression by immigrant donor T cells in the thymus has been noted previously in adults^{30,42}, but not in neonates³⁵. It is clear that much more needs to be learned about the control of T cell immigration into the thymus. In particular, it would be interesting to understand whether expression of CCR7, known to be important for medullary access by developing thymocytes^{21,22}, is also required for efficient reentry of mature peripheral T cells into the thymic medulla.

WHAT PROMOTES LYMPHOCYTE IMMIGRATION INTO THE THYMUS?

Under what conditions is thymic immigration of mature T cells enhanced? The neonatal thymus is very permeable to both naive and previously activated CD4 and CD8 T cells^{26,35}. Within a day after injection of $5\text{--}10 \times 10^6$ naive adult T cells, 2–5% of the mature (CD24^{low}) SP compartment of the host thymus was comprised of transferred cells in week old neonates³⁵. Thymus lobes from aged mice are also much more leaky to naive T cells than are those from young adults⁴⁰. While an average of 600 cells lodged in the young adult thymus after intravenous injection of $6\text{--}8 \times 10^6$ naive CD8 T cells, approximately 6,500 cells homed to the thymus of 70–76 week old recipients⁴⁰. This permeability is unlikely to be due solely to the sparse DP compartment found in the aged thymus. Thus, irradiation and cortisone injection, known to deplete the DP compartment, failed to promote the thymic immigration of naive T cells in young adults, although irradiation did increase the frequency of previously activated cells reentering the thymus³³.

Certain disease states have also been shown to promote thymic immigration by recirculating T cells. Mature resting T cells readily enter the atrophic thymus of T cell deficient SCID mice, and persist there for months³⁴. Lymphopenia induced by deletion of the pre-T α gene or by the generation of radiation bone marrow chimeras engineered such that thymic output is approximately 1% of normal levels both increase migration to the thymus of mature T cells⁴¹. At the opposite end of the spectrum, the hyperplastic thymus of AKR mice is similarly permissive to immigrating mature T cells. In this case, an increase in the number of medullary blood vessels expressing appropriate addressins has been identified as the likely driving force behind this influx^{59,60}. In another model, intravenously injected T cells localize to the thymus lobes of old (but not young) (NZB x SJL) F₁ mice, correlating with the onset of disease in this autoimmune-prone strain⁵⁰.

Setting aside the findings in hyperplastic AKR thymuses and aged (NZB x SJL) F₁ mice, which analyze the immigration of mature T cells that may themselves display aberrant characteristics, T cell lymphopenia characterizes each of the conditions shown to promote enhanced donor T cell migration into the thymus. Why this might be has not been experimentally addressed.

DO RECIRCULATING LYMPHOCYTES SERVE A FUNCTION IN THE THYMUS?

Why are the thymic lobes of individuals across many species permeable to mature T cells? The preferential migration of activated relative to naive T cells into the thymus and their long term persistence within this organ have led to the notion that the thymus may serve as a repository of T cell memory^{28,45}. A parallel function for the B cell generative compartment, the bone marrow, has been supported by considerable experimental evidence^{61–64}. What would be the advantage of selective recruitment of memory T cells into the thymus and bone marrow? This sheltered environment may protect the memory pool from cytokine deprivation, environmental insult, or triggers of homeostatic proliferation. It could also help rid the generative organs of infected cells that could negatively select antigen-reactive thymocytes, most needed in the periphery during an infection. Thus, retaining some memory T cells within the thymus could

help keep this generative organ free of foreign antigens and ensure the development of new antigen-specific T cells during times of need.

A role in tolerance induction has also been ascribed to immigrating T cells within the thymus. The permeability of the neonatal thymus to naive T cells facilitates the intrathymic induction of tolerance to superantigens expressed by injected CD8 T cells, as measured by the deletion of reactive thymocytes⁶⁵. A similar function has been ascribed to allogeneic T cells experimentally introduced into the adult³⁹. Thus, induction of self-tolerance among developing thymocytes to antigens expressed primarily by mature T cells might benefit from the reentry of antigen-expressing mature T cells into the thymus. Conversely, migration into the thymus of self-activated T cells may promote the deletion of those cells upon encounter with their cognate antigens in the thymus. For example, T cells that develop in young individuals and are specific for antigens expressed only in the adult may be more easily deleted upon encounter with the relevant antigen while sequestered within the thymus^{38,48}. It has also been proposed that T cells can acquire self-antigens that they recognize, and through their migration into the thymus, present these passively acquired antigens in tolerogenic form to developing T cells^{33,44}.

It is apparent that there is considerable crosstalk between positively selected thymocytes and medullary thymic epithelial cells. Thus, formation of a medullary compartment requires the presence of mature thymocytes⁶⁶. Reentering mature T cells may also alter the stromal environment within the thymus by helping regulate the size and integrity of the medullary thymic epithelial cell compartment³⁴. The close apposition of the thymic vasculature and medullary epithelial cells is also of interest¹⁷, as it is through this area that mature T cells are likely to enter. Given the importance of the thymic medullary epithelial compartment for inducing self tolerance⁵⁻⁷, immigrating mature T cells may indirectly help regulate autoimmunity by influencing the thymic environment. In fact, recent evidence indicates that mature CD4 T cells (SP thymocytes in these experiments) help regulate the expansion of medullary thymic epithelial cells expressing tissue specific antigens^{67,68}. It is these cells that have been implicated in negative selection. It is still unknown whether reentering CD4 T cells can serve this same function.

The recently recognized potential for mature Tregs to migrate into the thymus has renewed the debate on the potential intrathymic function for immigrating T cells. Parabiosis between wildtype mice and those lacking the gene encoding the preT α chain of the pre-TCR demonstrated that Tregs found in the thymus of the latter mice originated predominantly from the pool of recirculating Tregs derived from the wildtype partner⁴¹. The depletion of peripheral CD4⁺ Tregs in anti-CD4 antibody transgenic mice has revealed that at least 20% of thymic Tregs are likely derived from the pool of recirculating Tregs that reenter the thymus⁴³. The use of RAG2p-GFP transgenic mice has also enabled the characterization of immigrating mature (GFP⁺) T cells within the thymus of unmanipulated individuals. Approximately 50% of thymic Tregs were found to be GFP⁻ nonproliferating cells, and therefore represent reentering peripheral T cells^{42,55}. It is not clear what intrathymic function can be ascribed to these returning Tregs, but a role in tolerance induction is attractive, given their ability to control self-reactivity among peripheral T cell populations⁸.

One final intrathymic function has been proposed for mature T cell immigrants. Recent work has suggested that reentering mature T cells expressing the requisite MHC class I molecules can positively select CD8⁺ T cells expressing a uniform TCR⁵⁶. In these experiments, positive selection was defined as the appearance of mature CD8 SP thymocytes, while the appearance of functional T cells was not analyzed. Despite the somewhat inefficient appearance of these mature CD8 SP thymocytes, this work offers an exciting addition to the repertoire of functions performed by mature T cells that manage to reenter the thymus, and may help explain how

functional T cell immunity can be achieved under experimental conditions in which hematopoietic cells differentiate in mismatched thymic epithelial compartments⁵⁶. Table 1 summarizes each of the potential functions outlined above that returning peripheral T cells might serve as they masquerade as thymocytes.

CONCLUDING COMMENTS

The well-documented immigration of mature T cells into the thymus has required us to alter our earlier views that this generative organ has evolved in part to provide a foreign antigen- and mature cell-free zone to promote thymocyte maturation without environmental insult. We now know that mature CD4 and CD8 T cells do return to the thymus, and that their reentry is facilitated by prior activation. The means by which these cells enter the thymus, and the reasons why their immigration is apparently promoted in adults under lymphopenic conditions and in neonates are currently unknown. Several non-mutually exclusive functions have been proposed for these migrants, including roles in providing a repository for memory T cells, eliminating foreign antigen in the thymus during times of infection, inducing negative selection to antigens they express or passively acquire, maintaining medullary thymic epithelial cells, providing a population of Tregs exposed to tissue-specific antigens in the lymphoid periphery, and mediating positive selection.

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Figure 1. T cell development proceeds through the checkpoints of β selection, positive selection, and negative selection as developing thymocytes migrate through distinct thymic microenvironments. Reentering mature T cells may intersect this pathway, possibly impacting both positive and negative selection

(a) and (i) Progenitor cells and mature peripheral T cells both likely enter the thymus through post-capillary venules at the cortico-medullary junction. Developing thymocytes (depicted as light blue cells) follow the migration patterns detailed below, while reentering mature peripheral T cells (depicted as dark blue cells) persist mainly, although not exclusively, in the medulla. (b) Developing T cells migrate to the outer cortex of the thymus and recombine TCR β chain genes. Successful generation of a TCR β chain drives cells to (c) proliferate and (d) co-express CD4 and CD8 coreceptors, and migrate deeper into the cortex. (e) DP thymocytes rearrange TCR α gene segments. Surface expression of the resulting TCR $\alpha\beta$ molecules is required for positive selection, driven most efficiently by low-affinity interaction with self-MHC complexes on cortical thymic epithelial cells (cTECs). Positively selected cells will commit to the appropriate CD8 or CD4 T cell lineage. (f) The resulting SP thymocytes migrate into the medulla. In the medulla (g), expression of tissue-specific antigens by medullary thymic epithelial cells (mTECs) and presentation of self-antigens by dendritic cells (DC) enforce central tolerance by the clonal deletion of self-reactive SP thymocytes. (h) Mature

CD4SP and CD8SP thymocytes likely exit via the post-capillary venules at the cortico-medullary junction.

Figure 2. Mature peripheral T cells recirculate to the thymus of unmanipulated mice

Thymocytes from RAG2p-GFP mice were analyzed by flow cytometry for cell surface markers and GFP. (a) Representative dot plots from an approximately 70 week old mouse, showing that populations gated as CD4SP (left) and CD8SP (right) contain GFP⁺ SP thymocytes and GFP⁻ mature T cells that have reentered the thymus. (b) Cells gated as CD4SP (left) and CD8SP (right) were counterstained with the indicated antibodies to reveal the cell surface phenotype of GFP⁻ (open histograms) and GFP⁺ cells (filled histograms). The GFP⁻ populations consist of predominantly mature (CD24^{low}Qa2^{hi}) and previously activated (CD44^{hi}) cells. (c) The percent of the total SP thymic compartment comprised of reentering peripheral T cells increases with age. (d) The number of GFP⁻ mature T cells found in the thymus initially increases and then remains relatively stable with age.

Table 1
Possible Roles for Mature T cells that Recirculate to the Thymus

Function	References
Provide a repository for memory T cells	Naparstek, 1982; Fink, 1984; Gopinathan, 2001
Eliminate foreign antigens from the thymus during an infection	Naparstek, 1982; Fink, 1984
Induce negative selection to antigens they express	Webb, 1990; Surh, 1993; Tian, 2004
Induce self tolerance in the returning, activated T cells themselves	Ben-Nun, 1982; Chau, 2002
Induce negative selection to antigens they passively acquire through their TCRs	Agus, 1991; Gopinathan, 2001
Maintain medullary thymic epithelial cells	Surh, 1992; Hikosaka, 2008; Irla, 2008
Provide the thymus with Tregs that have been exposed to antigens in the periphery	Bosco, 2006; McCaughtry, 2007; Zhan, 2007; Weinreich, 2008
Mediate positive selection	Kirberg, 2008