Antigen Receptor Revision as a Mechanism of Peripheral T Cell Tolerance

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Tolerance induction among mature T cells in the lymphoid periphery operates through many mechanisms, including the induction of anergy and cell death. By a newly described pathway, $CD4^+$ T cells that encounter a tolerogen are either deleted or are driven to reexpress the proteins that mediate DNA recombination and to rearrange and express diverse novel antigen receptor genes encoding proteins that no longer recognize the tolerogen. T cells that have successfully completed such receptor revision are both functional and self-tolerant. The broad antigen receptor repertoire that results from receptor revision benefits the individual faced with decreasing $CD4^+$ T cell counts due to elimination of T cells recognizing a widespread self-antigen that cannot be cleared. However, reexpression of the recombinase machinery in mature peripheral T cells offers the potential for illegitimate recombination and subsequent dysregulation of cellular functions. Why would such a risky venture be undertaken? Perhaps the down-regulation of receptor expression that precedes revision decreases the basal level of signaling through the receptor, signaling that is critical for T cell survival. The cell may interpret this loss of signaling capacity as a developing thymocyte would, by generating alternate antigen receptors whose expression levels are conducive to cell survival. In this way, receptor revision may recapitulate thymocyte maturation.

ABBREVIATIONS

TCR	T cell receptor
MHC	Major histocompatibility complex
RAG	Recombination activating gene
Tg	Transgenic
$V\beta^{endo}$	Endogenously derived TCR Vβs
Mtv	Mammary tumor virus
GFP	Green fluorescent protein
GC	Germinal center

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Introduction

The immune system is charged with the dual tasks of defense against invading pathogens and preservation of self. For T cells, carrying out these simultaneous duties requires careful discrimination between self and nonself, a distinction whose borders are constantly reassessed throughout the lifetime of the cell. Of clear importance to T cell function is the nature of the T cell receptor (TCR) for antigen, a heterodimeric cell surface molecule monoclonally expressed by each individual T cell. The TCR recognizes short peptide antigens bound to a groove within molecules encoded by the major histocompatibility complex (MHC) or to longer glycoproteins called superantigens, presented outside the peptide-binding groove of the MHC.[1,2] One of the 1st challenges facing developing T cells within the thymus, the organ in which T cells mature, is the assembly of diverse TCRs through recombination of the separate gene elements that together encode this protein.[3] TCR-α and TCR-β gene rearrangement occurs by a developmentally regulated process mediated by the products of recombination activating gene 1 (RAG 1) and RAG 2.[4] The TCR repertoire is selected within the thymus for recognition of the multitude of peptide antigens presented by self-MHC molecules and culled of overt self-reactivity.[5] This latter intrathymic process, termed negative selection, requires that thymocytes be exposed to the relevant self antigens.[6] Although intrathymic expression of antigens once believed to be strictly tissue specific has recently expanded the pool of known contributors to negative selection,[7] alternate forms of tolerance induction must exist to handle mature peripheral T cells recognizing age-dependent or tissue-specific antigens.

SUPERANTIGENS

Virally or bacterially encoded glycoproteins presented outside the groove of major histocompatibility complex class II molecules and recognized by the T cell receptor primarily through its Vβ domain.

Although intrathymic negative selection operates primarily to eliminate overtly self-reactive thymocytes through programmed cell death, the induction of tolerance among mature peripheral T cells has been shown to operate through many pathways.[8] Autoreactive T cells may be prevented from encountering antigen in a context that could lead to cell activation.[9] On the other hand, these T cells may meet antigen and be rendered anergic (nonfunctional) to further stimulation through their TCRs.[10] Anergic T cells generally have a shortened life span and may appear phenotypically normal or may express reduced surface levels of TCR and/or CD4 or CD8 coreceptor molecules. Self-reactive cells may be directly eliminated without traversing an anergic state, or may be driven into terminal differentiation, thereby temporarily exhausting the supply of antigen-reactive cells.[11] The activity of autoaggressive T cells may also be suppressed by veto cells,[12] antigen-specific regulatory T cells,[13] or nutrient deprivation in specialized sites such as the maternal-fetal interface.[14] What follows is a review of a novel form of tolerance induction by which mature, peripheral $CD4^+$ T cells reinitiate rearrangement of TCR loci to transform a self-reactive TCR into one that is self-tolerant. This tolerance mechanism, termed TCR revision, rescues self-reactive lymphocytes and generates from them a diverse population of functional, self-tolerant $CD4^+$ T cells. However, TCR revision is a risky form of tolerance induction, as it entails potential illegitimate DNA rearrangement events and generation of TCRs outside the selective thymic microenvironment.

Summary:

- Although intrathymic negative selection operates primarily to eliminate overtly self-reactive thymocytes, the induction of tolerance among mature peripheral T cells operates through many pathways.
- Through the process of TCR revision, mature peripheral $CD4^+$ T cells can be driven to reinitiate DNA rearrangement within the TCR loci and express diverse, newly generated, nonautoreactive TCRs.
- The decision to upregulate RAG expression and undergo TCR revision may be a byproduct of T cell maturation.
- The surprisingly broad TCR repertoire that results from TCR revision is an obvious benefit to the individual faced with decreasing $CD4^+$ T cell counts due to elimination of cells recognizing a self-antigen it is unable to clear.
- Reexpression of the recombinase machinery in mature peripheral T cells offers the potential for aberrant juxtaposition of cellular oncogenes and lymphocyte-specific promoters.

A Weak Tolerogen Can Drive Peripheral $CD4^+$ T Cells Down Alternate Pathways of Death and Antigen Receptor Revision

The majority of T cells from young mice carrying a functionally rearranged TCR-β chain transgene express that gene, constituting a population of T cells expressing diverse TCR-α chains paired with a uniform, transgene-encoded TCR-β chain.[15] In Vβ5 transgenic (Tg) mice, transgene expression among $CD8^+$ T cells remains high at all ages. However, Vβ5 expression among $CD4^+$ peripheral T cells decreases with age and, concomitantly, expression of TCR-β chains encoded by rearranged endogenous genes increases.[16] The lymphoid periphery of Vβ5 Tg mice is also characterized by a striking age-dependent inversion of the CD4:CD8 ratio. Both the inversion of the CD4:CD8 ratio (caused by the loss of $CD4^+$ peripheral T cells) and the loss of transgene expression (caused by the appearance of cells expressing endogenous Vβs or $Vβ^{endo}$) are dependent on a superantigen encoded by a defective endogenous mammary tumor virus-8 (Mtv-8).[17] Expression of the Mtv-8-encoded superantigen appears to be confined to the lymphoid periphery and provides for an unusually weak interaction with $Vβ5^+$ TCRs.[18]

The interaction between $Vβ5^+CD4^+$ T cells and MHC class $II^+Mtv\text{-}8^+$ cells drives the T cell partner down 1 of 2 tolerance pathways (Fig. 1). The $CD4^+$ T cell can be rendered anergic and die, thereby effecting an inversion of the CD4:CD8 ratio, or it can be rescued by losing Mtv-8 reactivity upon extinction of Vβ5 surface expression. This latter

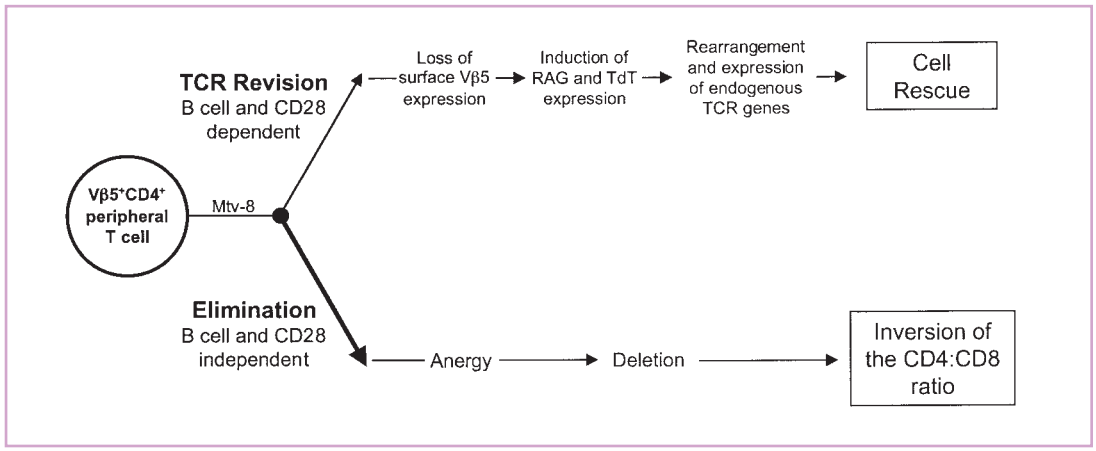

Figure 1. Schematic diagram of the alternate pathways to tolerance for mature $CD4^+$ T cells in Vβ5 transgenic mammary tumor virus-8 ($Mtv\text{-}8^+$) mice. $V\beta5^+CD4^+$ T cells that encounter Mtv-8 in the lymphoid periphery either become anergic and die or revise their T cell receptors (TCRs), thereby eliminating Mtv-8 reactivity. T cells that undergo TCR revision express a diverse repertoire and contribute to the self-tolerant, functional T cell pool. RAG = recombination activating gene, TdT = terminal deoxynucleotidyl transferase.

NEGATIVE SELECTION

Elimination of overtly autoreactive T cells within the thymus as a means of inducing central tolerance (tolerance of immature lymphocytes within a generative organ).

pathway is called TCR revision because the loss of Vβ5 surface expression occurs hand in hand with the acquisition of endogenously derived TCR-β chains.[19] T cells from Vβ5 Tg mice do not undergo TCR revision in the absence of either B cells or CD28 molecules,[20,21] and revision appears to be highly inefficient in lethally irradiated $Mtv\text{-}8^+$ hosts whose hematopoietic systems have been reconstituted with bone marrow from $Mtv\text{-}8^+$ donors (C. J. McMahan and P. J. Fink, unpublished observations). In contrast, the deletional pathway is fully operative in Vβ5 Tg mice lacking B cells or CD28 molecules, and after lethal irradiation and bone marrow reconstitution. Thus, encounter with the same weak tolerogen can drive $CD4^+$ T cells down alternate pathways, leading to cell deletion or cell rescue through TCR revision.

TCR Revision Results in Expression of a Diverse, Self-Tolerant Receptor Repertoire

The TCR repertoire of $V\beta^{endo+}V\beta5^-CD4^+$ T cells from $Mtv\text{-}8^+$ Vβ5 Tg mice is so diverse that it effectively recreates the nontransgenic TCR-β chain repertoire within each individual mouse.[21] This diversity is apparent even at the molecular level, of individual rearrangements of 1 particular Vβ gene element to 1 particular Jβ element. These newly generated TCRs can deliver proliferative signals upon antibody-mediated cross-linking and are therefore fully functional. $V\beta^{endo+}CD4^+$ T cells from Vβ5 Tg mice do not appear to be autoreactive, either in vivo or in vitro.[21]

Cells Undergoing Revision Are Acutely Activated, TCR^{low}, and Recombination Competent

As $Mtv\text{-}8^+$ Vβ5 Tg mice age, they accumulate $V\beta5^{low}$ cells within the $CD4^+$ T cell compartment, and it appears to be these cells that are undergoing TCR revision. $V\beta5^{low}$ cells are $CD44^{high}$ and $CD62L^{low}$, both markers consistent with an activated T cell phenotype (Table 1). However, unlike antigen-activated lymphocytes, $V\beta5^{low}$ cells are $Thy\text{-}1^{low}$ and express both RAG1 and RAG2.[20] The presence of recombination intermediates within the TCRα and β loci in these unusual cells indicates both that the RAG1 and RAG2 gene products are functional and that the TCR loci are accessible to the recombinase.[20] To more easily focus only on T cells undergoing TCR revision, the Vβ5 transgene has been crossed onto a line of mice Tg for green fluorescent protein (GFP) under the control of the RAG2 promoter.[22] Cells from these mice glow green when RAG2 is expressed. $GFP^+CD4^+V\beta5^{low}$ peripheral T cells from these $Mtv\text{-}8^+$ RAG reporter mice are larger than their $GFP^+V\beta5^{high}$ counterparts and are $CD45RB^{high}$, both markers of acutely activated rather than memory cells (Table 1). Although

Table 1 | **Relative Size and Surface Phenotype of Naive or Antigen-Experienced CD4⁺ T Cells**

	Type of Mature CD4⁺ T Cell			
Marker	Naive	Acutely Activated	Revising	Memory
Size	Small	Large	Large	Small
T cell receptor	High	Low	Low	High
Thy-1	High	High	Low	High
CD45RB	High	High	High	Low
CD62L	High	Low	Low	Low
CD44	Low	Low	High	High
CD69	Low	High	Low	Low
CD25	Low	High	Low	Low

this small population of cells appears to be acutely activated, expression of the transient activation markers CD69 and CD25 does not appear to be significantly up-regulated. Thus, T cell interaction with a weak tolerogen that leads to TCR revision appears to initiate some but not all of the events associated with full activation of T cells encountering a foreign conventional antigen.

Cells whose phenotype is consistent with their position as intermediates in a TCR revision process have also been reported in normal humans[23] and, in increased numbers, in patients with defective responses to DNA damage.[24] These $CD4^+$ peripheral T lymphocytes are TCR^{low}, RAG-expressing cells that contain recombination intermediates at the TCR-β loci. It is unclear whether these cells are undergoing TCR revision and, if so, what triggers this response.

Revision Targets Mature Peripheral T Cells

Several observations indicate that TCR revision is a peripheral event targeting mature T cells. $V\beta^{endo+}V\beta5^-CD4^+$ T cells, the products of TCR revision, appear with similar kinetics in both thymectomized and unmanipulated Mtv-8^+ Vβ5 Tg mice.[25] Conversely, $V\beta^{endo+}V\beta5^-CD4^+$ thymocytes cannot be detected in mice at any age, although the diversity of the expressed endogenous TCR repertoire and the minimal mouse-to-mouse variation in this diversity together suggest that their generation is not a rare event.[21] Sequence analyses of revised TCR-β chain genes indicate that they contain regions of nontemplated nucleotides that are atypical of those generated in the adult thymus.[21] Most definitively, GFP Tg Vβ5 Tg mice that have been thymectomized more than 4 weeks previously can generate $GFP^+V\beta^{endo+}V\beta5^-CD4^+$ T cells, and these cells are acutely activated and RAG-expressing. Together, these results indicate that through the process of TCR revision, mature peripheral $CD4^+$ T cells can be driven to reinitiate recombination within the TCR loci and express newly generated, nonautoreactive TCRs.

TCR Revision Is Not Limited to TCR Tg Mice

Although using TCR Tg mice has the obvious benefit of creating an artificial situation in which a uniformly expressed TCR is known to interact with a given self-antigen and in which the TCR expression history is known for T cells that can be physically tracked, this artificiality brings with it a set of caveats. It is therefore important to stress that TCR revision is not limited to ectopic, multicopy transgene-encoded receptors. Work from the Kanagawa lab demonstrates that TCR revision in response to recognition of exogenous superantigen can occur within the normally configured TCR-α locus.[26] Furthermore, it has been shown recently that in Mtv-8^+ Vβ5 nontransgenic GFP Tg RAG reporter mice thymectomized at least 4 weeks previously, a significantly greater proportion of $V\beta5^+$ cells are GFP^+ relative to $V\beta5^-$ or $V\beta8^+$ cells. These findings indicate that Mtv-8-driven RAG-mediated TCR revision occurs even in TCR nontransgenic mice. The appearance of $CD4^+TCR^{low}RAG^+$ T cells in normal humans also suggests that TCR revision occurs in individuals carrying normal TCR loci. Thus, the notion that a weak tolerogen can initiate TCR revision appears to be generalizable to unma-

nipulated individuals. However, it should not be inferred from these studies that TCR revision is a common response to tolerogen encounter in the lymphoid periphery. Outside of the Vβ5$^+$CD4$^+$ population of mature T cells, the frequency of GFP$^+$ T cells in the RAG reporter mice is very low (less than 2%). TCR revision may be initiated within a narrow window defined by TCR/superantigen affinity, superantigen expression levels, or frequency of encounter between T cells and superantigen-expressing cells.

TCR Revision May Be Induced by Encounter with Superantigens but Not Conventional Antigens

In recently published experiments, Huang et al.[26] initiated RAG expression and TCR-α chain revision in TCR Tg animals injected with spleen cells expressing a viral superantigen (Mtv-6) capable of interacting with the transgenic TCR. Similar to the Vβ5/Mtv-8 system described above, this TCR revision resulted in the gradual appearance of CD4$^+$ T cells no longer expressing the transgenic TCR, although in these mice expression of the TCR-α chain, rather than the TCR-β chain, was gradually lost. Although this distinction is likely due to the configuration of the TCR loci in these engineered mice (the TCR-α transgene was incorporated within the endogenous TCR-α locus, and subsequent rearrangement events would thereby physically eliminate the TCR-α and not the TCR-β transgene), it does emphasize that revision at both the TCR-α and TCR-β loci is possible. It is still unclear whether both genetic regions are equally accessible to the recombinase. Interestingly, Huang et al. failed to induce TCR revision in these same animals immunized not with Mtv-6$^+$ cells but with cells expressing cytochrome c, the foreign antigen recognized in the context of self-MHC by the transgenic TCR-αβ molecules.[26] These striking results remain to be generalized by data from other conventional antigen/superantigen systems, but they may point to distinct biological outcomes resulting from recognition of these 2 classes of antigens. It is unclear whether these distinctions result from differences in the type of antigen-presenting cell, the affinity of the TCR/ligand interaction, the frequency of these interactions, or some qualitatively different signal transmitted by a TCR bound to a conventional peptide antigen presented in the groove of MHC[1] versus that same receptor bound to a superantigen presented outside the MHC-antigen-presenting groove.[2]

PERIPHERAL TOLERANCE

Tolerance induced by multiple mechanisms among mature lymphocytes in the lymphoid periphery.

Potential Risks and Benefits of TCR Revision

As a tolerance mechanism, TCR revision appears to be a risky proposition. Reexpression of the recombinase machinery in mature peripheral T cells offers the potential for aberrant juxtaposition of cellular oncogenes and lymphocyte-specific promoters.[27,28] Such genome instability can result in dysregulated cellular functions and transformation. It is not clear yet whether TCR revision increases the risk of oncogenesis. However, a relationship between the increased frequency of TCR^{low}RAG$^+$ CD4$^+$ peripheral T cells in ataxia telangiectasia and Nijmegen breakage syndrome patients and their frequent lymphoma-specific chromosomal translocations has been suggested.[24] TCR revision may also serve to modulate T cell reactivity to superantigen-expressing bacterial or viral pathogens.[26] Loss of superantigen reactivity could influence the outcome of an infection with such an organism.[29-32] A further danger in TCR revision lies in the fact that by not eliminating the autoreactive cell outright, the individual exposes itself to the possibility of continued autoaggression. Although the end product of TCR revision is a population of cells that appears to be self-tolerant,[20,21] it is unclear whether the revision process itself is associated with stringent selection against overt self-reactivity, as in the thymus during T cell maturation, or whether subsequent selection events in the lymphoid periphery are called into play to eliminate newly generated autoreactive T cells. Regardless of the means of selection, this secondary process is unlikely to be infallible. Why, then, would evolution select such risk-taking behavior?

The surprisingly broad TCR repertoire that results from TCR revision is an obvious benefit to the individual faced with decreasing CD4$^+$ T cell counts due to elimination of cells recognizing a self-antigen it is unable to clear. The benefits of receptor revision may therefore outweigh the risks, although the age dependency of TCR revision makes it likely that these benefits are enjoyed most commonly by mice 5 to 6 months of age, well past the

age of sexual maturity. One solution to this conundrum may be that the decision to up-regulate RAG expression and undergo TCR revision is a by-product of T cell maturation. During thymocyte development, RAG expression is maintained and TCR loci remain accessible to the recombinase until the proper signals are delivered into the cell through a functional TCR.[33] In the absence of such a signal, TCR rearrangement continues.[34] One of the first phenotypic changes apparent in cells undergoing TCR revision is the partial loss of TCR expression at the cell surface.[20] In fact, following this TCR^{low} trait alone led to the isolation of RAG-expressing $CD4^+$ T cells from human donors.[23,24] Perhaps this down-regulation, whether ligand mediated or not, serves to decrease the basal level of signaling through the TCR, signaling that is thought to be key for T cell survival.[35,36] The cell may interpret this loss of signaling capacity in the same way a developing thymocyte would—by up-regulation of RAG expression and generation of alternate TCR genes whose protein products will be tested for their signaling capacity. Thus, rather than being selected for directly, TCR revision may be a by-product of the way in which the TCRs expressed by developing thymocytes are selected to meet the dual requirements for self-tolerance and recognition of foreign peptides in the context of self-MHC molecules. The added flexibility in immune recognition provided to the aging mouse by TCR revision could then be considered an unexpected bonus.

T CELL RECEPTOR REVISION

One mechanism of tolerance induction among mature peripheral $CD4^+$ T cells in which an autoreactive T cell receptor is replaced with a non-self-reactive T cell receptor.

Unanswered Questions

How does the same weak tolerogen drive $CD4^+$ T cells down distinct pathways leading to cell elimination, on one hand, and cell rescue through TCR revision, on the other?

No definitive experiments have yet shed light on this question, although the B cell requirement for TCR revision may be informative.[20] One viable hypothesis suggests that cell death requires a strong signal delivered to a T cell, perhaps by a dendritic cell, while the signal that initiates TCR revision would be delivered by a B cell, a less potent antigen-presenting cell. The exact nature of the TCR-α chain paired with the Tg TCR-β chain may also modulate the strength of signal delivered by a particular superantigen.[37-39] In support of this argument, the TCR-α chain repertoire of Vβ5 Tg mice has been shown to vary with age, becoming less diverse as Vβ5 expression decreases.[17]

How is TCR revision triggered?

If further experiments substantiate the notion that superantigens but not conventional antigens can induce reactive T cells to undergo TCR revision, it becomes important to understand how these cellular interactions differ. The phenotype of the cells actively engaged in revision suggests that one initial trigger may be an interaction that initiates partial, but not complete, cellular activation. All work to date does suggest that one important characteristic of cells undergoing revision is their TCR^{low} status,[20,23,24] although how this phenotype is achieved is still unclear.

Where does TCR revision take place?

The germinal center (GC) offers one potential site for TCR revision that is consistent with all available data. At this point, only $CD4^+$ and not $CD8^+$ T cells have been shown to undergo TCR revision.[20,23,26] $CD4^+$ T cells can enter GCs, whereas $CD8^+$ T cells are excluded.[40,41] TCR revision, but not cellular elimination, requires B cells[20] and CD28 molecules[21] both known to be required for efficient GC formation. GC T cells are Thy-$1^{low\ and}$ are activated,[42] as are cells undergoing TCR revision. The GC provides a niche in which B cells undergo stringent selection on the basis of their expressed antigen receptors. It is conceivable that such a selective microenvironment could impose self-tolerance on a population of $CD4^+$ T cells expressing newly generated TCRs. Using the RAG reporter mice, it should now be possible to pinpoint the location of those T cells undergoing antigen receptor revision.

Is TCR revision associated with an increased risk of autoimmunity, illegitimate recombination, or susceptibility to pathogens thought to express superantigens?

It is these 3 areas that are most likely to be affected negatively by TCR revision. Will cells undergoing TCR revision be found at the site of tissue-specific autoimmunity? Can the expression of *RAG* genes in T cells within the lymphoid periphery lead

to chromosomal translocations within the TCR loci? Will the loss of superantigen reactivity in T cells increase an individual's susceptibility to pathogens expressing superantigens?

Clearly, many key questions remain to be answered as this newly discovered means of peripheral T cell tolerance induction is explored.

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