Review

The Qa-1 Dependent CD8$^+$ T Cell Mediated Regulatory Pathway

Hong Jiang[1, 2]

The immune system has evolved a variety of regulatory mechanisms to ensure the peripheral self-tolerance as well as the optimal capacity to elicit effective anti-infection immunity. At present, there is no satisfactory conceptual framework to explain how the peripheral immunity is regulated at a biological system level, which enables the immune system to perform its essential functions to mount effective immunity to virtually any foreign antigens but avoid harmful immune responses to self. In this regard, during the past few years, an "affinity/avidity model of peripheral T cell regulation" has been proposed and tested, which opens up a new paradigm to understand how the peripheral immunity, to both self and foreign antigens, is regulated. The paradigm is based on the discovery of a subset CD8$^+$ T cells with TCRs which specifically recognize a unique set of self-peptides presented by the MHC class Ib molecule Qa-1 differentially expressed on T cells as a function of the affinity/avidity of T cell activation. These Qa-1 restricted CD8$^+$ T cells represent an example of how the immune system utilizes a unified mechanism to regulate adaptive immunity to both self and foreign antigens. Thus, by selectively down-regulating T cells of intermediate affinity/avidity, to any antigens, the immune system controls the adaptive immunity without the necessity to distinguish self from non-self in the periphery at the level of T cell regulation. *Cellular & Molecular Immunology*. 2005;2(3):161-167.

Key Words: T cell regulation, CD8$^+$ T cell, affinity/avidity, Qa-1, TCR

Introduction

The immune system has evolved a variety of regulatory mechanisms mediated by distinct T subsets of regulatory cells to ensure that the immune system performs its essential functions of maintaining self-tolerance while permitting effective immunity to any foreign pathogens (1, 2). The regulation mediated by these regulatory T cell subsets is superimposed on intrinsic regulatory mechanisms including antigen activation induced apoptosis, anergy as well as the differentiation of naïve T cells into Th subsets secreting regulatory cytokines. Among the regulatory T cell subsets are CD4$^+$ and CD8$^+$ T cells as well as NKT cells. The focus of this article is to introduce and summarize the function of Qa-1 dependent CD8$^+$ T cell mediated regulatory pathway in control of peripheral immunity and the potential impact of this pathway on our current understanding of the peripheral T cell regulation.

The Qa-1 dependent CD8$^+$ T cells

The Qa-1 dependent regulatory CD8$^+$ T cells were first identified by studies seeking to define the mechanisms by which CD8$^+$ T cells participate in the resistance induced by the first episode of experimental allergic encephalomyelitis (EAE). In the EAE model induced by 1-9Nac myelin basic protein (MBP) in B10PL mice, the first episode of EAE renders the animals highly resistant to the re-initiation of EAE by secondary immunization. This resistance is CD8$^+$ T cell dependent because mice that recovered from EAE and then were depleted of CD8$^+$ T cells developed EAE upon re-immunization with 1-9Nac MBP (3). Furthermore, mice depleted of CD8$^+$ T cells during the initial induction of EAE and allowed to recover normal levels of CD8$^+$ T cells are not resistant and develop EAE again upon re-challenge with 1-9Nac MBP. Thus, CD8$^+$ T cells require priming during the first episode of EAE to regulate CD4$^+$ T cells triggered by the secondary MBP stimulation *in vivo*. Moreover, when CD8$^{-/-}$ (KO) mice are bred with the EAE susceptible PL/J strain, the CD8$^{-/-}$ mice develop more chronic EAE than the wild-type PL/J mice, reflected by a higher frequency of relapses (4). These experiments provide evidence that CD8$^+$ T cells play a key role in both inducing resistance to autoimmune EAE and abrogating recurrent relapsing episodes of auto-immunity *in*

[1]Department of Medicine, Division of Rheumatology, College of Physicians & Surgeons, Columbia University, USA;

[2]Corresponding to: Dr. Hong Jiang, Department of Medicine, Division of Rheumatology, College of Physicians & Surgeons, Columbia University, 630 W. 168th Street, PH 8-E Ste.101, New York, NY 10032, USA. Tel: +01-212-305-9988, Fax: +01-212-305-4943, E-mail: HJ4@columbia.edu.

Received Jun 3, 2005. Accepted Jun 10, 2005.

vivo.

It was further demonstrated that T cell vaccination with certain MBP reactive $CD4^+$ T cell clones induces both $CD8^+$ T cell dependent protection from EAE and the emergence of $CD8^+$ T cells capable of recognizing MBP reactive $CD4^+$ T cell clones in a Qa-1 restricted manner. The specific recognition can be blocked by antibodies to Qa-1, CD8 and the αβTCR (5-7). These data suggest that the interaction between the regulatory $CD8^+$ T cells and target $CD4^+$ T cells is through the recognition of Qa-1/self-peptide complex expressed on $CD4^+$ T cells by αβTCR on regulatory $CD8^+$ T cells. In addition, the Qa-1 restriction of regulatory $CD8^+$ T cells has not only been observed in the down-regulation of Qa-1 expressing $CD4^+$ T cells in superantigen and self-antigen induced T cell immune responses as described above (5) but also shown by Cantor et al. in the regulation of antibody synthesis in which Qa-1 expressing B cells were shown to induce regulatory $CD8^+$ T cells (8).

It is known that a significant number of self-reactive T cell clones escape thymic negative selection and are released into the periphery where some are potentially pathogenic. Employing the murine EAE model of auto-immunity it was demonstrated that one mechanism for limiting the outgrowth of potentially pathogenic self-reactive clones in the periphery is the selective down-regulation of these clones by $CD8^+$ T cells (9). It was shown that superimposed on other homeostasis mechanisms, during the evolution of auto-immunity in EAE, $CD8^+$ T cells are induced which fine tune the peripheral self-reactive T cell receptor (TCR) repertoire. The MBP reactive TCR repertoire was assayed in naïve, EAE recovered mice as well as EAE recovered mice depleted of $CD8^+$ T cells by TCR Vβ surface expression, CDR3 length distribution and CDR3 sequencing analysis. In EAE recovered mice, certain MBP autoreactive $CD4^+V\beta8.2^+$ clones are significantly decreased compared with naïve mice and this decrease is not observed if $CD8^+$ T cells were depleted from these mice. The clones that persist in $CD8^+$ T cell intact mice are highly diverse in contrast to the clones expanded in $CD8^+$ T cell depleted mice, which are dominated by the significant outgrowth of a few clones. Importantly, the T cell clones that expand in the absence of $CD8^+$ T cell control are enriched in potentially pathogenic self-reactive T cell clones capable of inducing EAE *in vivo*. Thus, these *in vivo* and *vitro* studies provide evidence that $CD8^+$ T cells only selectively down-regulate certain but not all self-reactive T cells within the TCR Vβ8.2 family. These regulatory $CD8^+$ T cells play a key role in controlling self-reactive TCR repertoire by selectively down-regulating the potentially pathogenic self-reactive T cell clones which are included in the T cell population with higher growth potential responding to self-antigen MBP in the periphery (9).

The biological function of the Qa-1 dependent $CD8^+$ T cell pathway has been further confirmed in recent studies of Qa-1 "knockout" mice, which were used to directly study, *in vivo,* the role of Qa-1 in the regulatory pathway mediated by $CD8^+$ T cells in the control of auto-immunity (10). For example, it was demonstrated that the Qa-1-deficient mice develop severe EAE when exposed to the self PLP peptide

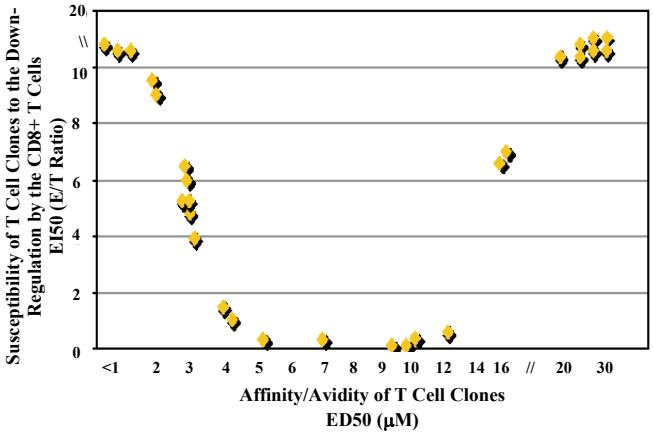

Figure 1. Qa-1 dependent $CD8^+$ T cells selectively down-regulate activated T cell clones based on their affinity/avidity.

and fail to develop resistance to EAE that normally develops in wild-type mice after immunization with PLP peptide. Furthermore, the failure of resistance to EAE is associated with the escape of Qa-1-deficient CD4 cells from $CD8^+$ T cell suppression. Moreover, these studies also show that the effect of Qa-1 on the function of regulatory $CD8^+$ T cells in the control of autoimmune disease *in vivo* is primarily observed during the secondary, but not the primary immune response.

An "affinity/avidity model of peripheral T cell regulation"

To further understand the mechanisms employed by the $CD8^+$ T cells to selectively down-regulate certain but not all activated T cells, the studies were extended to a conventional antigen Hen Egg Lysozyme (HEL) system (2). Because HEL represents a foreign antigen in wild type (WT) mice but a self-antigen in HEL transgenic (TG) mice, this system permits direct studies of the cellular and molecular mechanisms by which the $CD8^+$ T cells control the peripheral TCR repertoire to both self and foreign antigens. It was shown that Qa-1 dependent $CD8^+$ T cells are biologically involved in both the development of the peripheral tolerance to the self-antigen HEL in HEL TG mice as well as the affinity maturation of T cells to foreign antigen HEL in WT mice. The regulatory $CD8^+$ T cells were observed to inhibit the immune response to HEL when it functions as a self-antigen in HEL TG mice but enhance the immune response to the same antigen when it functions as a foreign antigen in WT mice. The studies showed that the *in vivo* unresponsiveness, or tolerance, to HEL, measured by T cell proliferation, in HEL TG mice is broken by *in vivo* treatment with mAbs to CD8 or Qa-1. Furthermore, $CD8^+$ T cells from HEL TG mice suppress the HEL response when adoptively transferred *in vivo* or mixed with HEL reactive T cells *in vitro*.

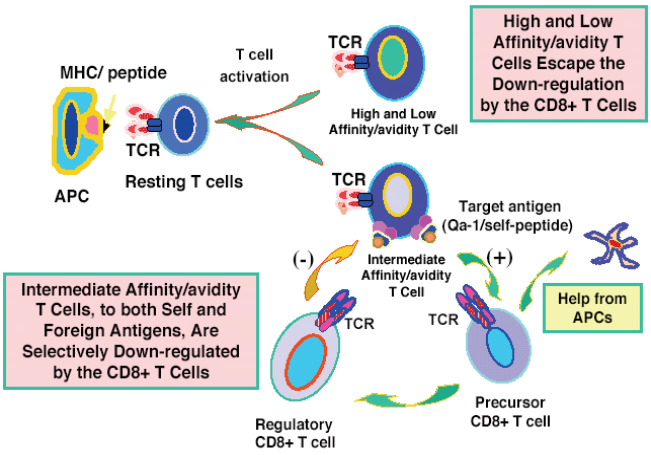

Figure 2. The affinity/avidity model of peripheral T cell regulation by the Qa-1 dependent CD8$^+$ T cells.

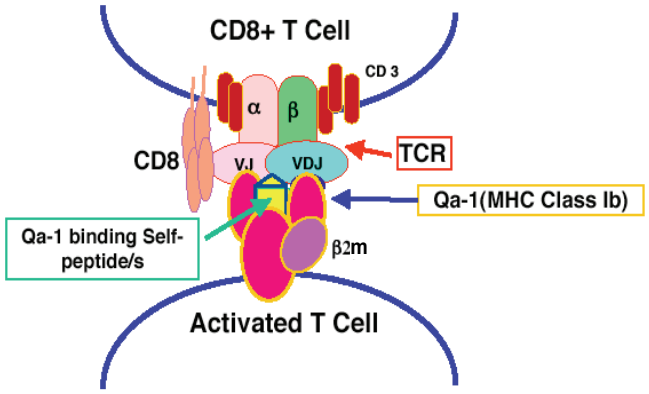

Figure 3. Tri-molecular interaction between Qa-1 dependent CD8$^+$ T cell and target T cell.

In addition, a panel of HEL reactive CD4$^+$ T cell clones of different affinity/avidity was assayed for their susceptibility to the down-regulation by the CD8$^+$ T cells in a T cell inhibition assay. The results showed that the CD8$^+$ T cells preferentially down-regulate T cell clones of intermediate, but not high or low, affinity/avidity to HEL. Figure 1 depicts the functional relationship between the affinity/avidity of 28 T cell clones measured by ED_{50} and their susceptibility to down-regulation by the CD8$^+$ T cells measured by EI_{50}. In these assays, the ED_{50} is the antigen dose needed to reach the half maximum proliferation in a standard T cell proliferation assay and the EI_{50} is the effector to target ratio needed for half maximum inhibition in a CD8$^+$ T cell inhibition assay. Importantly, the specific down-regulation was blocked by the mAbs to Qa-1, TCR and CD8 molecules. We thus concluded that CD8$^+$ T cells play a crucial role in the establishment and maintenance of the peripheral self-tolerance to HEL in HEL TG mice by selectively down-regulating T cell clones of intermediate affinity/avidity to self-antigen HEL.

The role of CD8$^+$ T cells in regulating HEL response in WT mice was further studied where HEL functions as a foreign antigen and elicits a vigorous secondary response to HEL characterized by increased overall affinity/avidity during T cell affinity maturation. The studies showed that treatment with mAbs to CD8 or Qa-1 abrogates the affinity maturation *in vivo*. Employing TCR CDR3 sequence analysis, we observed a strong correlation between the changes of overall affinity/avidity induced by *in vivo* treatment with mAbs to CD8 and Qa-1 and the frequencies of certain canonical CDR3 motifs found in the HEL repertoire. These unique motifs were identified in a panel of HEL specific T cell clones with known affinity (ED_{50}) and known susceptibility to CD8$^+$ T cell mediated down-regulation (EI_{50}). The studies provide experimental evidence that CD8$^+$ T cells facilitate T cell affinity maturation by selectively down-regulating T cells of intermediate, but not high or low, affinity/avidity to HEL. Thus, CD8$^+$ T cells facilitate T cell affinity maturation to foreign antigen HEL in WT mice employing the same mechanism used to ensure self-tolerance to HEL, which functions as a self-antigen in TG mice.

These *in vitro* and *in vivo* studies have thus led to the formulation of an "affinity/avidity model of peripheral T cell regulation" in which the susceptibility of activated T cells to the down-regulation by the CD8$^+$ T cells is determined by the affinity/avidity of the initial T cell activation (2). This regulatory pathway is composed of a series of sequential cellular events. As illustrated in Figure 2, it is initiated by the activation of naïve T cells during the primary immune response in which the TCR on T cells interacts with MHC/ antigen peptide complexes presented by conventional APCs. One of the consequences of the initial T cell activation is the differential expression of a specific "target antigen", which, at least, includes the "Qa-1/self-peptide complex", on the surface of target T cells. Importantly, the expression of the "target antigen", which is recognized by the TCR on regulatory CD8$^+$ T cells, is determined by the affinity/avidity during T cell activation, regardless of which antigen the target T cells are triggered by. In this regard, since T cells are not professional APCs, the professional APCs, such as dendritic cells may be recruited and function to provide co-stimulatory molecules during the induction phase of the regulatory CD8$^+$ T cells. The "target antigen" expressed on certain activated T cells triggers the regulatory CD8$^+$ T cells to differentiate into effector cells, which in turn down-regulate any activated T cells expressing the same target antigen. A characteristic feature of the Qa-1 dependent CD8$^+$ T cells is that they require priming by the activated T cells during the primary immune response in order to regulate the secondary immune response. This distinguishes the CD8$^+$ pathway from other cellular regulatory pathways, including the NKT and the CD4$^+$CD25$^+$ regulatory T cells, which exist as naturally occurring suppressor cells (1-3, 7, 9). In addition, since the only distinguishable phenotype between the Qa-1 dependent CD8$^+$ T cells and the conventional CD8$^+$ T cells is the usage of a distinct set of αβTCRs which specifically recognize Qa-1/

self-peptide complex differentially expressed on susceptible target T cells, it is unlikely that Qa-1 dependent $CD8^+$ T cells represent a lineage specific $CD8^+$ T cell population.

The molecular interaction between the $CD8^+$ T cells and the target T cells is through the recognition of self-peptide/s presented by a MHC class Ib molecule Qa-1 on target T cells and TCR on the $CD8^+$ T cells (Figure 3). In this regard, a number of biologic features of the Qa-1 molecule make it particularly interesting to its role as a restricting element in immunoregulation. First, Qa-1 is preferentially expressed on activated, but not resting, T cells (11). Moreover, because Qa-1 expression on activated T cells is short lived this excludes resting T cells from down-regulation by Qa-1-dependent $CD8^+$ T cells. Second, Qa-1 is of limited polymorphism with the potential to present self and foreign peptides to $CD8^+$ T cells. The predominant self-peptide presented by Qa-1 is Qdm, a hydrophobic peptide derived from deader sequence of MHC class Ia molecules (12-15). This peptide (AMAPRTLLL) binds with high affinity and accounts for the majority of the peptides associated with Qa-1 which complex bind to NKG2A on NK cells and inhibit NK activity (15, 16). We call Qdm or Qdm like peptides type A peptides. However, Qa-1 can also bind other self-peptides including those derived from heat shock proteins (17) and pre-proinsulin leader sequences (18), which do not bind to NKG2A, and are called type B peptides. We hypothesize that some of the type B peptides may be the targets for the $CD8^+$ T cells. Since the clones of high and low affinity/avidity are not subject to the $CD8^+$ T cell regulation, the most straight forward explanation of why only intermediate affinity/avidity T cells are susceptible to the $CD8^+$ T cell down-regulation is due to the differential expression of certain Qa-1/type B self-peptide complexes as a function of affinity/avidity. It is possible that in the intermediate affinity/avidity clones T cell activation results in the expression of certain type B Qa-1 binding peptides, which compete with Qdm or Qdm like peptides, for binding to Qa-1 and interact with the TCR on the $CD8^+$ T cells. Thus the differential expression of Qa-1/B peptide versus Qa-1/type A peptide, which can not be distinguished by staining with the antibody to Qa-1, may play a crucial role in determining the susceptibility of the activated T cells to the down-regulation by the $CD8^+$ T cells (2).

The impact of the "affinity/avidity model" on our current understanding of the regulation of the peripheral immunity

The pioneering work of Burnet and Medawar demonstrated that introducing a foreign antigen to animals during the neonatal period induces immunological tolerance to that foreign antigen and the animal will not make immune response to reject the same antigen during adulthood (19, 20). Thus, exposure of the immune system to foreign antigens during the embryonic development leads to a state of tolerance to that antigen. These studies suggested that the definition of self versus non-self is arbitrary to the immune system because foreign antigens presented during fetal life are thereafter considered self. Since biologically, only self-antigens are "seen" by the immune system during embryonic stage, developing lymphocytes that are potentially self-reactive, by interacting with self-antigens during embryonic development become tolerant to self. Since then a tremendous amount of work has been done to understand the mechanisms of self-tolerance. For example, direct evidence has emerged that thymocytes expressing TCR of high affinity/avidity for MHC/self-peptide complexes undergo apoptosis and are deleted centrally in the thymus (21, 22).

Nevertheless, increasing evidence indicates that both central thymic and peripheral extra-thymic mechanisms are important. For example, studies have shown that some self-reactive T cells with lower or intermediate affinity/avidity to self-antigen escape thymic negative selection and are released into the periphery (9, 23, 24). Although these self-reactive T cell clones display lower affinity/avidity to MHC/self-peptide complexes, compared with truly high affinity/avidity self-reactive T cell clones, they are capable of self-peptide driven proliferation and some may differentiate into potentially pathogenic effector cells (2, 9, 25). To avoid pathogenic auto-immunity various peripheral regulatory mechanisms have evolved to fine tune the self-reactive TCR repertoire and suppress the clonal expansion of those self-reactive clones with TCRs of affinity/avidity that are not sufficiently high to be eliminated intrathymically, but high enough to induce pathogenic auto-immunity. Thus, under normal circumstances, despite the abundance of self-reactive clones in the periphery, clinical auto-immunity is usually well controlled.

The peripheral regulatory mechanisms involve mechanisms intrinsic to the antigen activation and differentiation of T cells as well as exogenous mechanisms mediated by regulatory "suppressor" T cells. The intrinsic mechanisms include antigen activation induced cell death (26) and antigen induced expression of co-stimulatory molecules including CD40L, CD80, CD86 and CTLA-4, which dictate whether immunity or anergy ensues (27-30). A third general set of regulatory mechanisms, is the functional activation and differentiation of the $CD4^+$ T cells into the distinct Th1 and Th2 subsets (31-33) or Tr1 and Tr3 subsets (34-36) phenotypically distinguished, in part, by the elaboration of distinct sets of cytokines. These intrinsic mechanisms have evolved to dictate not only the magnitude but also the class of immune response generated (33, 37-43). Superimposed on these intrinsic mechanisms of homeostatic regulation are the exogenous regulatory mechanisms mediated by distinct T subsets of regulatory NKT, $CD4^+$ and $CD8^+$ T cells, which dominantly suppress the outgrowth of potentially pathogenic self-reactive T cells in the periphery (44).

There remains a fundamental conceptual and practical problem that needs to be dealt with by all regulatory mechanisms, which normally operate in the periphery. If the immune system controls potential pathogenic auto-immunity by suppression, does it also suppress the normal immune responses to foreign antigens, which are essential for effective immunity to infectious pathogens? If it does, what would be the biological consequences of such suppression?

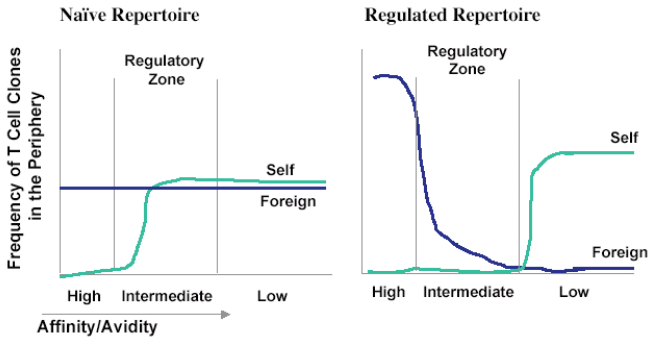

Figure 4. Selective down-regulation of intermediate affinity/avidity T cells by the CD8$^+$ T cells shapes the peripheral T cell repertoire to both self and foreign antigens during the evolution of immune response.

At present there is no satisfactory conceptual framework to explain how the peripheral immunity is regulated at a biological system level, which enables the immune system to perform its essential functions. In this regard, the "affinity/avidity model of peripheral T cell regulation", we have proposed and tested during the past few years, opens up a new paradigm to understand how peripheral immunity, to both self and foreign antigens, is regulated during the adaptive immunity. The paradigm is based on the discovery of a subset CD8$^+$ T cells with TCRs which specifically recognize a unique set of self-peptides presented by the MHC class Ib molecule Qa-1 differentially expressed on T cells as a function of the affinity/avidity of T cell activation. These Qa-1 restricted CD8$^+$ T cells represent an example of how the immune system utilizes a unified mechanism to regulate adaptive immunity to both self and foreign antigens (2). In this regard, it is known that the affinity/avidity of TCR to self-antigen is the basis of the central thymic negative selection and thus profoundly influences the formation of the naïve peripheral TCR repertoire to both self and foreign antigens. During the negative selection high affinity/avidity self-reactive T cells are deleted in the thymus (21, 22). Clearly, a biological function of this central negative selection of high affinity/avidity self-reactive clones is to eliminate the "immediate danger" of pathogenic auto-immunity in the periphery. However, to provide sufficiently large size of mature T cell pool to ensure the maximum flexibility of the peripheral repertoire to foreign antigens, in addition to the low affinity/avidity self-reactive T cells, thymic negative selection allows certain intermediate affinity/avidity self-reactive T cells to be released into the periphery (9, 23, 24). As a consequence, the peripheral self-reactive repertoire is truncated and primarily composed of intermediate and low affinity/avidity self-reactive clones. On the other hand, the TCR repertoire to foreign antigens is composed of clones covering the entire spectrum of high, intermediate and low affinity/avidity. Because the compositions of the naïve peripheral TCR repertoires to self and foreign antigens are different due to thymic negative selection, the biological consequences of the selective down-regulation of the intermediate affinity/avidity T cells to self and foreign antigens are also different (see Figure 4). Preferential down-regulation of the intermediate/avidity clones provides a mechanism to control the "potential danger" of pathogenic auto-immunity mediated by the T cell clones enriched in the pool of intermediate affinity/avidity self-reactive T cells in the periphery (9). The same mechanism is also used to preserve and select for clones with high affinity/avidity to foreign antigens, which are essential for effective immunity to infectious pathogens (2).

Taken together, the conceptual framework of the "affinity/avidity model" offers a few unique insights, which challenge our conventional ways of thinking and might change the current paradigms relating to how the peripheral immunity is regulated.

1. The "affinity/avidity model" proposes that the specificity of the regulation is not at the level of antigens which activate the target T cells. The specificity is at the level of recognizing or sensing the consequence of activation of T cells determined by the affinity/avidity during the initial T cell activation, regardless of which antigens the target T cells are triggered by. Because this recognition is blocked by mAbs to Qa-1, it suggests that the actual target structure that is recognized by the CD8$^+$ T cells is likely to be certain self-peptides, presented by Qa-1, differentially expressed on target T cells as a function of affinity/avidity. Since the diversity of self-peptides binding to Qa-1, which are responsible for rendering T cells susceptible to the down-regulation by CD8$^+$ T cells, is limited, this model enables the immune system to efficiently regulate immune response to countless self and foreign antigens in a powerful but simple way.

2. The model demonstrates that the immune system employs a unified mechanism of suppression to regulate peripheral immunity to both self and foreign antigens, which appears to have opposing effects: preserving tolerance to "self" while facilitating T cell affinity maturation to "foreign". Because the compositions of the naïve peripheral TCR repertoires to self and foreign antigens are different due to thymic negative selection, the biological consequences of selective down-regulation of the intermediate affinity/avidity T cells to self and foreign antigens are also different (2). This forms the conceptual framework for a new paradigm to explain, at a biological system level, how the immune system regulate peripheral immunity to both self and foreign antigens without the necessity to distinguish self from non-self in the periphery at the level of T cell regulation (2).

3. The conceptual framework of "affinity/avidity model" may also well be suited for other peripheral regulatory pathways, for example, CD4$^+$CD25$^+$ regulatory T cells, which currently dominate the field of immune regulation, but the specificity of the regulation by the CD4$^+$CD25$^+$ T cells is unclear (42, 45-47). It is conceivable that the CD4$^+$ Tregs may, like the Qa-1 restricted CD8$^+$ regulatory cells, preferentially down-regulate activated T cells on the basis of the affinity/avidity but employ different recognition and effector mechanisms.

Acknowledgements

The research was supported by NIH grants AI39630, U19 AI/DK46132 and National Multiple Sclerosis Society grant RG2938A.

References

1. Jiang H, Chess L. The specific regulation of immune responses by CD8+ T cells restricted by the MHC class Ib molecule, QA-1. Annu Rev Immunol. 2000;18:185-216.
2. Jiang H, Wu Y, Liang B, et al. An affinity/avidity model of peripheral T cell regulation. J Clin Invest. 2005;115:302-312.
3. Jiang H, Zhang SI, Pernis B. Role of CD8+ T cells in murine experimental allergic encephalomyelitis. Science. 1992;256:1213-1215.
4. Koh DR, Fung-Leung WP, Ho A, Gray D, Acha-Orbea H, Mak TW. Less mortality but more relapses in experimental allergic encephalomyelitis in CD8-/- mice. Science. 1992;256:1210-1213.
5. Jiang H, Ware R, Stall A, Flaherty L, Chess L, Pernis B. Murine CD8+ T cells that specifically delete autologous CD4+ T cells expressing Vβ8 TCR: a role of the Qa-1 molecule. Immunity. 1995;2:185-194.
6. Jiang H, Kashleva H, Xu LX, et al. T cell vaccination induces T cell receptor Vβ-specific Qa-1-restricted regulatory CD8(+) T cells. Proc Natl Acad Sci U S A. 1998;95:4533-4537.
7. Jiang H, Braunstein NS, Yu B, Winchester R, Chess L. CD8+ T cells control the TH phenotype of MBP-reactive CD4+ T cells in EAE mice. Proc Natl Acad Sci U S A. 2001;98:6301-6306.
8. Noble A, Zhao ZS, Cantor H. Suppression of immune responses by CD8 cells. II. Qa-1 on activated B cells stimulates CD8 cell suppression of T helper 2 responses. J Immunol. 1998;160:566-571.
9. Jiang H, Curran S, Ruiz-Vazquez E, Liang B, Winchester R, Chess L. Regulatory CD8+ T cells fine-tune the myelin basic protein-reactive T cell receptor Vβ repertoire during experimental autoimmune encephalomyelitis. Proc Natl Acad Sci U S A. 2003;100:8378-8383.
10. Hu D, Ikizawa K, Lu L, Sanchirico ME, Shinohara ML, Cantor H. Analysis of regulatory CD8 T cells in Qa-1-deficient mice. Nat Immunol. 2004;5:516-523.
11. Tewarson S, Zaleska-Rutczynska Z, Figueroa F, Klein J. Polymorphism of Qa and Tla loci of the mouse. Tissue Antigens. 1983;22:204-212.
12. Aldrich CJ, Rodgers JR, Rich RR. Regulation of Qa-1 expression and determinant modification by an H-2D-linked gene, Qdm. Immunogenetics. 1988;28:334-344.
13. Aldrich CJ, Waltrip R, Hermel E, et al. T cell recognition of QA-1b antigens on cells lacking a functional Tap-2 transporter. J Immunol. 1992;149:3773-3777.
14. Lowen LC, Aldrich CJ, Forman J. Analysis of T cell receptors specific for recognition of class IB antigens. J Immunol. 1993;151:6155-6165.
15. Kurepa Z, Hasemann CA, Forman J. Qa-1b binds conserved class I leader peptides derived from several mammalian species. J Exp Med. 1998;188:973-978.
16. Cotterill LA, Stauss HJ, Millrain MM, et al. Qa-1 interaction and T cell recognition of the Qa-1 determinant modifier peptide. Eur J Immunol. 1997;27:2123-2132.
17. Imani F, Soloski MJ. Heat shock proteins can regulate expression of the Tla region-encoded class Ib molecule Qa-1. Proc Natl Acad Sci U S A. 1991;88:10475-10479.
18. Chun T, Aldrich CJ, Baldeon ME, Kawczynski LV, Soloski MJ, Gaskins HR. Constitutive and regulated expression of the class IB molecule Qa-1 in pancreatic β cells. Immunology. 1998;94:64-71.
19. Burnet M, Fenner F. Production of Antibodies (ed 2nd). Melbourne: McMillan; 1949.
20. Billingham RE, Brent L, Medawar PB. Activity acquired tolerance of foreign cells. Nature. 1953;172:603-606.
21. Kappler JW, Roehm N, Marrack P. T cell tolerance by clonal elimination in the thymus. Cell. 1987;49:273-280.
22. Hengartner H, Odermatt B, Schneider R, et al. Deletion of self-reactive T cells before entry into the thymus medulla. Nature. 1988;336:388-390.
23. Bouneaud C, Kourilsky P, Bousso P. Impact of negative selection on the T cell repertoire reactive to a self-peptide: a large fraction of T cell clones escapes clonal deletion. Immunity. 2000;13:829-840.
24. Sandberg JK, Franksson L, Sundback J, et al. T cell tolerance based on avidity thresholds rather than complete deletion allows maintenance of maximal repertoire diversity. J Immunol. 2000;165:25-33.
25. Kuchroo VK, Anderson AC, Waldner H, Munder M, Bettelli E, Nicholson LB. T cell response in experimental autoimmune encephalomyelitis (EAE): role of self and cross-reactive antigens in shaping, tuning, and regulating the autopathogenic T cell repertoire. Annu Rev Immunol. 2002;20:101-123.
26. Lenardo M, Chan KM, Hornung F, et al. Mature T lymphocyte apoptosis--immune regulation in a dynamic and unpredictable antigenic environment [In Process Citation]. Annu Rev Immunol. 1999;17:221-253.
27. Durie FH, Foy TM, Masters SR, Laman JD, Noelle RJ. The role of CD40 in the regulation of humoral and cell-mediated immunity. Immunol Today. 1994;15:406-411.
28. Klaus SJ, Pinchuk LM, Ochs HD, et al. Costimulation through CD28 enhances T cell-dependent B cell activation *via* CD40-CD40L interaction. J Immunol. 1994;152:5643-5652.
29. Koulova L, Clark EA, Shu G, Dupont B. The CD28 ligand B7/BB1 provides costimulatory signal for alloactivation of CD4+ T cells. J Exp Med. 1991;173:759-762.
30. Lenschow DJ, Walunas TL, Bluestone JA. CD28/B7 system of T cell costimulation. Annu Rev Immunol. 1996;14:233-258.
31. Coffman RL, Mosmann TR. CD4+ T-cell subsets: regulation of differentiation and function. [Review] [14 refs]. Res Immunol. 1991;142:7-9.
32. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. J Immunol. 1986;136:2348-2357.
33. Mosmann TR, Coffman RL. TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. Annu Rev Immunol. 1989;7:145-173.
34. Groux H, O'Garra A, Bigler M, et al. A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. Nature. 1997;389:737-742.
35. Levings MK, Roncarolo MG. T-regulatory 1 cells: a novel subset of CD4 T cells with immunoregulatory properties. J Allergy Clin Immunol. 2000;106:S109-112.
36. Roncarolo MG, Levings MK. The role of different subsets of T regulatory cells in controlling autoimmunity. Curr Opin Immunol. 2000;12:676-683.
37. Fitch FW, McKisic MD, Lancki DW, Gajewski TF. Differential regulation of murine T lymphocyte subsets. Annu Rev Immunol. 1993;11:29-48.
38. Seder RA, Paul WE. Acquisition of lymphokine-producing

phenotype by $CD4^+$ T cells. Annu Rev Immunol. 1994;12:635-673.
39. Charlton B, Lafferty KJ. The Th1/Th2 balance in autoimmunity. Curr Opin Immunol. 1995;7:793-798.
40. Del Prete G. The concept of type-1 and type-2 helper T cells and their cytokines in humans. Int Rev Immunol. 1998;16:427-455.
41. O'Garra A, Vieira P. Regulatory T cells and mechanisms of immune system control. Nat Med. 2004;10:801-805.
42. von Herrath MG, Harrison LC. Antigen-induced regulatory T cells in autoimmunity. Nat Rev Immunol. 2003;3:223-232.
43. Cohn M. Whither T-suppressors: if they didn't exist would we have to invent them? Cell Immunol. 2004;227:81-92.
44. Jiang H, Chess L. An integrated model of immunoregulation mediated by regulatory T cell subsets. Adv Immunol. 2004;83:253-288.
45. Shevach EM. Certified professionals: $CD4^+CD25^+$ suppressor T cells. J Exp Med. 2001;193:F41-46.
46. Sakaguchi S. Regulatory T cells: key controllers of immunologic self-tolerance. Cell. 2000;101:455-458.
47. Bach JF. Regulatory T cells under scrutiny. Nat Rev Immunol. 2003;3:189-198.