[Frontiers in Bioscience 13, 1062-1063, January 1, 2008]

A single clone of T cells may identify 'self' from 'non-self' through different recognition mechanisms

Yan-Ming Liu[1], Jing Luo[2], Di Chen[3]

[1]Tianjin University of Tradional Chinese Medicine, Tianjin, 300193, China, [2]Changchun University of Tradional Chinese Medicine, Changchun 130117, China, [3]Center for Musculoskeletal Skeletal Research, University of Rochester, Rochester, NY, USA

TABLE OF CONTENTS

1. ABSTRACT

T cell antigen recognition is a special process. The complicated bindings between T cell receptor (TCR) or co-receptor (CD4 or CD8) and antigen peptide-major histocompatibility complex (pMHC) molecules have specific physiological significance. Recent reports show that different recognition models do exist in recognizing pMHCs by a single T cell. These different recognition mechanisms allow a single T cell to identify 'self' from 'non-self' and result in different biological consequence.

2. DISCUSSION

The pattern of T cells recognizing and binding antigen peptide-major histocompatibility complex (pMHC) molecules through the receptor complex including T cell receptor (TCR) and the co-receptor (CD4 or CD8 molecule) is unique and different from other ligand/receptor recognition mechanisms. In $CD4^+$ T cells, the TCR binds both a peptide and the polymorphic region (α_1 and β_1 domain) of MHC-II molecule and CD4 molecule (as the co-receptor interacting with p56lck kinase) binds a constant region (β2 domain) of the MHC -II molecule at the same time (canonical model, Figure 1A). The recognition pattern of T cells is characterized by several features, such as MHC restriction and promiscuity or degeneracy (1), which are special and complicated. It seems that the restriction and the promiscuity will not be necessary for recognizing an invader and will cause the damage in recognizing efficiency or specificity in immune response. Thus, the question is whether evolution of the interactions between co-receptors and MHC molecules has any potential significance which remains to be investigated.

We know that there are different types of recognition patterns in T cells, including 'peptide-centric' and 'MHC-centric' types (2). Regarding to the function of CD4 molecules in the recognition of pMHCs in T cells, Vidal *et al.* demonstrate several types of T cell recognizing models (3). They generated CD4-deficient and $CD4^+$ cell lines of T cells, which express the same specific TCR. As a result, the $CD4^+$ T cells respond to both specific agonist peptides (high affinity agonists) and altered agonist peptides (low affinity agonists), and a CD4-deficient cell line (3.L2-ΔCD4) respond 'vigorously' to specific agonists but not to the altered agonist peptides.

Surprisingly, they found that CD4 could increase responsiveness of CD4-deficient cell line to high affinity agonists less, but to low affinity agonists better. Moreover this function of CD4 is dependent on its binding to MHC-II molecules, but not to $p56^{lck}$. These findings imply that there are different recognizing patterns for a single clone of T cells to pMHCs, including the TCR (without CD4) model (Figure 1B) and the TCR-CD4 (CD4 as a linker) model (Figure 1C), which are different from the canonical models.

A pseudodimer model (Figure 1D) has also been proposed (4). The basic signaling initial unit involves two TCRs, one or two CD4 molecule, one MHC molecule with an agonist, and a second MHC molecule with a self peptide. In this model, CD4 molecule serves as a linker and makes two TCRs dimerization to enhance biochemical singnaling (5). This model is supported by the finding that there are many endogenous pMHC molecules accumulated in the immunological synapse (the necessary structure for agonist pMHC to activate naïve $CD4^+$ T cells) and is consistent with several other reports (6,7).

Recently, Colf *et al.* (8) reported that a single TCR recognizes the self pMHC and foreign pMHC (cross-reacting or alloreactivity) by divergent mechanisms. It is speculated that the different basic recognition models may play a role in the development or differentiation of CD4+ T cells, the key master for both adaptive immune response to antigens (as 'non-self') and immune tolerance to other antigens (as 'self'). It has also been reported that T cell recognitions may induce the differentiation of T cells. Pennington *et al.* (9) examined the early events affecting T cell development in the thymus. They found that the propensity of early TCR-$\alpha\beta$ T-cell progenitors to Treg cells may be regulated at the double-negative stage (without CD4/CD8 molecule) of T cell development.

The different recognizing models of $CD4^+$ T cells simplify the explanation why or how specificity and promiscuity of its recognition, self tolerance and allograft reaction can coexist. We propose that it also suggest a possible mechanism for a vertebrate to differentiate 'self' from 'non-self' by a single $CD4^+$ T cell. At least if CD4 molecule plays divergent roles, such as in a TCR recognizing peptide packed homo-type MHC molecule as a

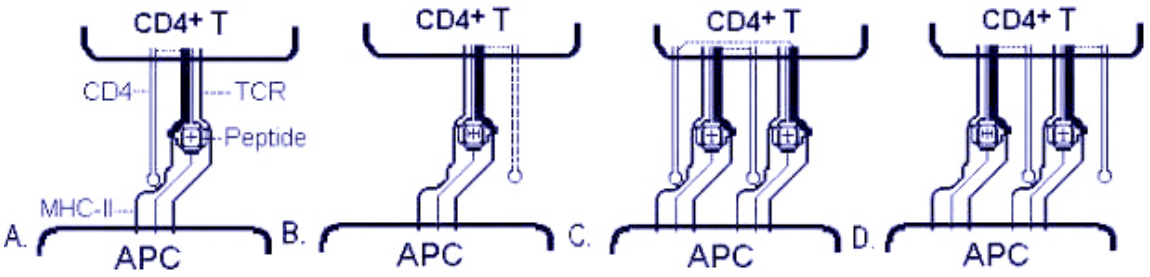

Figure 1. Patterns for the initial recognition of antigen peptide loaded MHC by T cells. In the canonical model (A), both a TCR and a CD4 molecule (as co-receptor) recognize a single pMHC molecule. In the TCR model (B), a TCR can recognize a pMHC molecule with specific peptide ligand. In the TCR-CD4 (CD4 as a linker) model (C), TCRs can recognize pMHCs molecule harboring a weak agonist peptide, and the CD4 molecule(s) serving as a linker to TCRs and forming a dimer. In the pseudodimer model (D), two TCRs binds an agonist pMHC and a lower-affinity peptide loaded MHC molecule respectively, and the CD4 molecule (as a linker) connects two TCRs molecules.

co-receptor but in the TCR recognizing peptide packed hetero-type MHC molecule (cross-reaction) as a linker, will offer different biological effects. It is apparent that the CD4 molecule as a co-receptor in T cell recognitions will interfere with the dimerization of TCRs, while the CD4 as a linker will promote TCRs to form a dimer or even a polymer and then initiate immune responses as found in many other receptor systems. This means that a single clone of CD4+ T cells may identify some 'self' type MHC from the other 'non-self' type MHC by different recognition models as there are different MHC molecules in a normal individual. This novel interpretation will help us understand the complicated immunology phenomena (10), such as the co-existence of negative selection and the development of nature Treg cells in the thymus, the immunological anergy and autoimmunity, the polymorphism of MHC molecules and MHC restriction. Most importantly, it will help us explain the origin and the evolution of immune system.

We have previously reported that the different MHC molecules might be the markers of the phase development or metamorphosis development and that the original function of the immune system is to regulate the metamorphosis in primary vertebrate (11-12). Taken together, all these theories will lead to the further investigation and better understanding the origin and mechanism of immune system.

3. REFERENCES

1. Eison H. N: Specificity and degeneracy in antigen recognition: yin and yang in the immune system. *Annu. Rev. Immunol.*, 19:1-21 (2001)
2. Rossjohn J & J. McCluskey: How a home-grown T Cell receptor interacts with a foreign landscape. *Cell*, 129:19-20 (2007)
3. Vidal K, C. Daniel, M. Hill, D. R. Littman & P. M. Allen: Differential requirements for CD4 in TCR-ligand interactions. *J. Immunol.*, 163:4811-4818 (1999)
4. Irvine D.J, M. A. Purbhoo, M. Korosgaard & M. M. Davis: Direct observation of ligand recognition by T cells. *Nature*, 419:845-849 (2002)
5.Hailman E & P. M. Allen: Slef help for T cells. *Nat. Immunol.*, 5:780-781 (2004)
6. Li Q.J, A. R. Dinner, S. Qi, D. J. Irvine, J. B. Huppa, M. M. Davis & A. K. Chakrabrty: CD4 enhances T cell sensitivity to antigen by coordinating Lvk accumulation at the immunological synapse. *Nat. Immunol.*, 5:791-799 (2004)
7. Korosgaard M, Q-J. Li, C. Sumen, J. B. Hupar & M. M. Davis: Agonisy/endogenous peptide-MHC heterodimers drive T cell activation and sensitivity. *Nature*, 434:238-243 (2005)
8. Colf L.A, A. J. Bankovich, N. A. Hanick, H. A. Bowerman, L. L. Jones, D. M. Kranz & K. C. Garcia: How a single T Cell receptor recognizes both self and foreign MHC. *Cell*, 129:135-146 (2007)
9. Pennington D. J, B. Silva-Santos, T. Silberzahn, M. Escorcio-Correia, M. J. Woodward, S. J. Roberts, A. L. Smith, P. J. Dyson & A. C. Hayday: Early events in the thymus affct the balance of effector and regulatory T cells. *Nature*, 444:1073-1077 (2006)
10. Liu Y-M & J. Luo: A novel interpretation about the immune recognitions of CD4+ T cells, *The Progress in Modern Biomedicine* (in Chinese),7:1-4 (2007)
11. Liu Y-M & J. Luo: Revaluation of the several important questions about immunology theory. *Immunology Journal* (in Chinese) 20(3):S133-S136. (2004)
12. Liu Y-M: The primitive function of the immune system. *Immunological Journal* (in Chinese), 11(1):61-63. (1995)

Key Words: T cells, Recognition, T cell receptor, histocompatibility complex, CD4, Review

Send correspondence to: Dr. Yan-Ming Liu, Tianjin University of Taditional Chinese Medicine, Tianjin, 300193, China, Tel: 86-22-2366-6045, Fax: 86-22-2305-1066, E-mail: lym2163@hotmail.com

http://www.bioscience.org/current/vol13.htm