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MHC restriction is imposed on a diverse TCR repertoire by CD4 and CD8 coreceptors during thymic selection

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Abstract

Mature $\alpha\beta$ T cells recognize foreign antigenic peptides presented by MHC molecules but do not recognize native antigenic proteins, features known as MHC-restriction. How MHC-restriction is imposed on $\alpha\beta$ T cells has intrigued immunologists for decades. One model proposes that germline-encoded elements in the TCR variable regions are evolutionarily conserved to only recognize MHC. However, we propose an alternative model that posits that MHC restriction is imposed by CD4 and CD8 coreceptors during thymic selection. Thus we think that TCRs are structurally able to recognize a huge diversity of ligands but only TCRs with MHC specificity survive thymic selection.

Basis of MHC restriction

MHC restriction is the cardinal feature of $\alpha\beta$ T cells and distinguishes $\alpha\beta$ T cells from all other immune cells. While both recognize foreign antigens, B cells recognize conformational antigenic epitopes on native antigenic proteins but $\alpha\beta$ T cells do not. MHC restriction refers to the fact that mature $\alpha\beta$ T cells recognize either lipids or peptides of antigenic proteins that are bound to MHC as peptide-MHC (pMHC) complexes, but essentially nothing else. Because pMHC complexes are membrane bound, MHC restriction prevents $\alpha\beta$ T cells from binding soluble antigens and focuses their receptors exclusively on cell surfaces. It is their exclusive focus on cell surfaces that makes it possible for CD8 T cells to identify and eliminate host cells either infected with intracellular pathogens or containing mutated cellular proteins, and for CD4 T cells to directly engage and collaborate with antigen-presenting cells to mount an adaptive immune response. Thus, MHC restriction is not a fortuitous feature of $\alpha\beta$ T cells but is necessary for the role they play in adaptive immunity.

As schematized in Figure 1, the germline organization of TCR and BCR gene loci resemble one another and both receptors utilize the same RAG proteins to mediate the random VDJ genetic rearrangements that lead to the production of functional TCR and BCR proteins [1, 2]. Nevertheless, BCRs are not limited in the biological structures that they can recognize as they can even recognize pMHC complexes in a peptide- and MHC-specific manner [3]. In contrast, mature $\alpha\beta$ T cells are constrained by MHC restriction to only recognizing pMHC complexes [4]. So what prevents TCRs from recognizing conformational antigenic epitopes

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on native proteins like BCRs, and what forces mature T cells to only express TCRs with pMHC specificities?

The germline model posits that MHC restriction is intrinsic to TCR structure because evolutionary pressures have conserved germline TCR sequences with the ability to bind MHC and have discarded germline sequences that are unable to bind MHC [5-11]. In support of this perspective, evolutionarily conserved germline-encoded amino acid residues have been identified in the CDR1 and CDR2 regions of some TCRs, and these not only contact MHC but are required for those TCRs to bind their pMHC ligands [6, 7]. These structural studies have provided important insights into how MHC-specific TCRs bind to pMHC ligands, but they do not allow the conclusion that all possible TCR rearrangements generate MHC-specific TCRs. Indeed, all TCRs that have been structurally analyzed to date were obtained from T cells that had previously undergone selection in the thymus to be MHC specific [12]. It will be important to perform similar structural analyses of TCR-ligand interactions on $\alpha\beta$ TCRs that had not been pre-screened in the thymus for MHC specificity. For a perspective on the opinion that TCR/MHC recognition is driven by germline-encoded interactions, see [ref] in this issue.

In contrast to the germline model, the selection model posits that evolution has not succeeded - and probably cannot succeed - in eliminating MHC-independent $\alpha\beta$ TCR specificities, so that $\alpha\beta$ TCRs possess the ability to recognize a diversity of ligands; however, thymic selection limits mature T cells to only expressing $\alpha\beta$ TCRs with specificity for pMHC complexes [13-15]. In our view, the MHC specificity of thymic selection is imposed by CD4 and CD8 coreceptors which promote signaling in the thymus by MHC-specific $\alpha\beta$ TCRs but prevent signaling by $\alpha\beta$ TCRs with other specificities (Figure 2). To assess the role of CD4 and CD8 coreceptors in imposing MHC specificity on thymic selection, we constructed experimental mice that lacked both CD4 and CD8 coreceptor proteins and additionally lacked MHC class I and class II expression (so-called Quad-KO mice) [15]. We hypothesized that the lack of CD4 and CD8 coreceptor proteins on Quad-KO thymocytes would permit signaling and selection of any $\alpha\beta$ TCRs that engaged a ligand in the thymus. In fact, mature Quad-KO $\alpha\beta$ T cells were strongly signaled in the thymus despite absent MHC and differentiated into mature T cells bearing a diversity of $\alpha\beta$ TCRs with unique ligand recognition specificities [15]. Unlike conventional $\alpha\beta$ T cells which only recognize and react to pMHC complexes on MHC-positive stimulator cells, Quad-KO $\alpha\beta$ T cells recognized and reacted to MHC-independent ligands expressed on MHC-null stimulator cells. Thus, it is our perspective that MHC restriction is not intrinsic to the germline-encoded structure of $\alpha\beta$ TCRs, but is imposed on the developing $\alpha\beta$ TCR repertoire during thymic selection.

TCR signaling and thymic selection

Like most immunological receptors, $\alpha\beta$ TCRs do not possess intrinsic kinase activity and cannot transduce intracellular signals by themselves. Instead, TCR signaling requires recruitment of Src-family protein tyrosine kinases Lck and Fyn, with Lck most important in developing thymocytes [16, 17]. Lck is a cytosolic protein that is post-translationally modified by fatty acids at its amino terminus which promotes its insertion into the inner leaf of the plasma membrane, as well as other membranes. Membrane-bound Lck can either remain 'free' of other membrane proteins or can be specifically bound by the cytosolic tails of the CD4 and CD8 coreceptor proteins [18-20]. Because it is not associated with other membrane proteins, free Lck can be brought into the TCR complex when TCRs engage external ligands to form microclusters which can passively capture free Lck. In contrast, CD4 or CD8 coreceptor-associated Lck is brought into the TCR complex only when the external domains of the TCR and coreceptor simultaneously engage the same extracellular

ligand [21, 22]. Because MHC molecules are the only extracellular ligands that CD4 and CD8 coreceptor proteins bind, MHC complexes are the only extracellular ligands that can simultaneously engage both TCR and coreceptor proteins. As a result, free Lck initiates signaling by $\alpha\beta$ TCRs regardless of their ligand specificities, but coreceptor-associated Lck only initiates signaling by $\alpha\beta$ TCRs that bind to pMHC complexes [23].

The association of Lck with CD4/CD8 coreceptors has two important consequences: it sequesters Lck to prevent signaling by $\alpha\beta$ TCRs that engage ligands other than MHC, and it promotes signaling by $\alpha\beta$ TCRs that engage MHC (Figure 2). Thus, it is the dual specificity of CD4/CD8 coreceptors for extracellular MHC and intracellular Lck that imposes MHC restriction on $\alpha\beta$ TCR signaling. Notably, the structure of a complete $\alpha\beta$ TCR–pMHC–CD4 ternary complex has recently been solved to reveal that $\alpha\beta$ TCR binding to pMHC complexes does permit CD4 coreceptors to simultaneously bind to the same pMHC complex [24].

So why would coreceptor sequestration of Lck in the thymus only impose MHC restriction on developing $\alpha\beta$ T cells but not $\alpha\beta$ T cells? The answer is that $\alpha\beta$ TCR complexes are expressed at an early stage in thymocyte development when thymocytes are coreceptor-negative (double negative, DN) and so contain free Lck. As a consequence, $\alpha\beta$ TCR signaling in DN thymocytes is not constrained by any requirement for MHC specificity [25]. In contrast, $\alpha\beta$ TCRs are expressed at a later stage in thymocyte development when thymocytes are coreceptor positive for both CD4 and CD8 (double positive, DP) which bind all the free Lck [15, 20]. As a result, $\alpha\beta$ TCR signaling in DP thymocytes is dependent on coreceptor-associated Lck.

Recognition of non-MHC ligands by $\alpha\beta$ TCRs

A few $\alpha\beta$ TCRs obtained from mature T cells have been identified over the years that bound to ligands independently of MHC, although they did so with very low apparent affinity [26–28]. Because of their very low binding affinity, it has been argued that their MHC-independent ligands were not their primary specificities and, therefore, such $\alpha\beta$ TCRs did not contradict the germline concept that MHC restriction was intrinsic to $\alpha\beta$ TCR structure. Indeed, these $\alpha\beta$ TCRs had been obtained from mature T cells that had undergone MHC-specific thymic selection and so likely were conventional MHC-restricted T cells with fortuitous (and rare) MHC-independent cross-reactivities. In contrast, $\alpha\beta$ T cells in Quad-KO mice did not undergo MHC-specific thymic selection and so expressed $\alpha\beta$ TCRs that were potentially very different from any $\alpha\beta$ TCRs previously studied.

Two $\alpha\beta$ TCRs derived from T-hybridoma cells that had been generated from Quad-KO T cells have been cloned, sequenced, and studied [14, 15]. The two $\alpha\beta$ TCRs were composed of different TCR α and TCR β chains which, by sequence, were not strikingly different from those composing conventional $\alpha\beta$ TCRs. What was unique about these two $\alpha\beta$ TCRs was that they both recognized native CD155, the murine analog of the human polio virus receptor, and they did so independently of MHC [14]. They did not require their CD155 protein ligand to be processed or presented by antigen presenting cells, as they recognized purified recombinant CD155 proteins immobilized on plastic. The two Quad-KO $\alpha\beta$ TCRs recognized different conformational CD155 epitopes, both of which were dependent on proper protein folding and both of which were affected by heat denaturation [14]. Importantly, the binding affinity for CD155 of the one $\alpha\beta$ TCR that was solubilized and re-folded was ~200nM, which was an equivalent affinity to that of primary antibodies but was an affinity that was 10-to-100 fold higher than that of conventional $\alpha\beta$ TCRs for pMHC ligands [29]. Thus, not having undergone MHC-specific thymic selection, the two $\alpha\beta$ TCRs displayed antibody-like recognition specificities [14].

The molecular basis for ligand recognition by these CD155-specific $\alpha\beta$ TCRs was also analyzed and revealed a major surprise. As expected, CD155 recognition depended on specific CDR3 sequences and so was mediated by the $\alpha\beta$ TCR combining site [14]. Surprisingly, however, MHC-independent CD155 recognition was also dependent on the same germline encoded and evolutionarily conserved amino acid residues in the TCR β CDR2 region that have been hypothesized to impose MHC specificity on conventional $\alpha\beta$ TCRs [7, 30-32]. That is, mutating these same amino acid residues abrogated or substantially diminished binding to CD155. Either this is a completely coincidental finding or it indicates that these germline encoded amino acid residues may have been conserved throughout evolution to permit or promote binding of any ligand to the $\alpha\beta$ TCR combining site, not just MHC. Structural studies will be required to clarify the significance of this surprising result. In any case, this finding contradicts the concept that evolutionarily conserved TCR residues uniquely promote $\alpha\beta$ TCR binding to MHC and are the molecular basis for MHC restriction.

Why were the two MHC-independent $\alpha\beta$ TCRs both specific for CD155? This is a question for which there is no definitive answer yet. One possibility is that CD155 may be a predominant specificity of $\alpha\beta$ TCRs generated in the absence of MHC-specific thymic selection and so is an important ligand. However, polyclonal $\alpha\beta$ T cells from Quad-KO mice do not display a skewed reactivity toward CD155, suggesting that CD155-specific $\alpha\beta$ TCRs are not actually over-represented among MHC-independent $\alpha\beta$ T cells [14]. Instead, we think that CD155-specific $\alpha\beta$ TCRs are only over-represented among Quad-KO T-hybridomas because the hybridoma fusion and cloning process downregulates CD155 protein expression, resulting in preferential survival of T-hybridomas expressing CD155-specific $\alpha\beta$ TCRs.

In summary, the finding of MHC-independent $\alpha\beta$ TCRs that bind conformational antigenic epitopes with high affinity contradicts the concept that MHC-restriction is intrinsic to the germline encoded structure of $\alpha\beta$ TCRs. Moreover, the generation of mature T cells expressing MHC-independent $\alpha\beta$ TCRs with antibody-like recognition specificities and affinities in Quad-KO mice is concordant with our concept that MHC-restriction is imposed during thymic selection as a result of coreceptor sequestration of Lck.

The preselection thymocyte repertoire

Because preselection DP thymocytes are shortlived, non-functional, and express relatively few surface $\alpha\beta$ TCRs, the ligand specificity of the preselection $\alpha\beta$ TCR repertoire is not straightforward to assess. Nevertheless, a few experimental attempts were made in the past to assess whether a bias toward MHC recognition exists among newly arising $\alpha\beta$ TCRs that have not been subjected to thymic selection [5, 8, 10, 11]. Such studies concluded that the preselection $\alpha\beta$ TCR repertoire did display a bias toward MHC recognition. We would point out, however, that these studies attempted to deduce the pre-selection $\alpha\beta$ TCR repertoire from the ligand reactivity of mature CD4 T cells. Notably, CD4 coreceptors, by sequestering Lck, promote signaling by MHC-specific $\alpha\beta$ TCR and impair signaling by MHC-independent $\alpha\beta$ TCR. Consequently, the results observed in these past experiments were undoubtedly affected by Lck sequestration and the MHC specificity of the CD4 coreceptors that the T cells expressed, and so likely did not reflect the actual diversity of the pre-selection $\alpha\beta$ TCR repertoire.

Nevertheless, we think that evolutionary pressures may well have biased the hugely diverse pre-selection $\alpha\beta$ TCR repertoire toward MHC recognition, but without substantially narrowing the diversity of ligands that $\alpha\beta$ TCRs can recognize. In fact, by limiting thymic selection to MHC-specific $\alpha\beta$ TCRs, CD4 and CD8 coreceptors would promote the

preferential retention in the germline of MHC-specific gene sequences. Thus, CD4 and CD8 coreceptors provide the evolutionary pressure for skewing germline TCR sequences toward MHC recognition.

In our perspective, the central role of CD4 and CD8 coreceptors in dictating the MHC specificity of thymic selection provides a powerful mechanism for driving the co-evolution of $\alpha\beta$ TCR with MHC. MHC molecules expand, mutate, and diversify throughout evolution, but so long as newly arising MHC molecules can bind CD4 and CD8 coreceptors, the thymus will select $\alpha\beta$ TCRs from the hugely diverse pre-selection repertoire that bind those new MHC molecules. However, in our mind, the presence of $\alpha\beta$ TCRs that can see future MHC ligands requires the maintenance of $\alpha\beta$ TCRs that may be unable to see current MHC molecules.

Concluding remarks

MHC restricted antigen recognition is normally a feature of all mature $\alpha\beta$ T cells. While evolutionary pressures would preferentially maintain germline sequences that contribute to MHC-specific $\alpha\beta$ TCRs, we think gene rearrangements give rise to $\alpha\beta$ TCRs that can recognize a huge diversity of ligands in addition to MHC. As a result, germline skewing of the $\alpha\beta$ TCR repertoire cannot explain why all mature $\alpha\beta$ T cells express MHC restricted $\alpha\beta$ TCRs. Instead, MHC restriction is the result of thymic selection that is made MHC-specific by thymocyte expression of CD4 and CD8 coreceptors.

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Outstanding Questions

- How diverse is the ligand recognition repertoire of MHC-independent $\alpha\beta$ TCRs?
- What are the selecting ligands in the thymus for MHC-independent $\alpha\beta$ TCRs?
- Are the signaling pathways induced by non-MHC ligands different from those induced by MHC-peptide ligands?
- Are the structures of MHC-independent TCR similar to MHC-specific TCRs?
- Because of their high affinity and MHC-independence, can MHC-independent $\alpha\beta$ TCRs be useful therapeutic reagents?

Figure 1.

Diversity of antigen recognition by antibodies and TCRs. Light and heavy immunoglobulin chains, as well as TCR α and TCR β chains, are composed of discrete Variable (V), Diversity (D), Joining (J) and Constant (C) gene segments. During B and T cell development, these diverse segments are joined by somatic recombination. Additional insertions, mutations (for Ig genes) and deletions add further diversity to yield a potential 10^{15} different Ig and TCR combinations. After protein synthesis, two pairs of light and heavy chains form a functional membrane-bound immunoglobulin peptide on B lymphocytes. The hugely diverse immunoglobulins can recognize and bind to conformational shapes on the surface of native antigens. Similarly, both TCR α and TCR β chains form a functional membrane-bound

heterodimer expressed on the surface of $\alpha\beta$ T cells. Before thymic selection, we think that TCR α and TCR β pairs recognize peptides bound to the Major Histocompatibility Complex (MHC) chains as well as native antigens. However, after thymic selection, $\alpha\beta$ T cells only express TCRs with MHC specificity.

Figure 2.

Coreceptor basis of MHC-specific thymic selection. TCR signaling requires the juxtaposition of Lck with TCR. In immature pre-selection $CD4^+CD8^+$ double positive (DP) thymocytes, all available tyrosine kinase Lck is coreceptor-associated and bound to the tails of both CD4 and CD8 coreceptors. Consequently, TCRs on pre-selection DP thymocytes can only access Lck when they bind to the identical pMHC complexes as CD4 and CD8 coreceptors. TCRs that bind MHC-independent native ligands cannot access coreceptor-associated Lck because the CD4 and CD8 coreceptors only bind to extracellular MHC complexes. Thus, only MHC-specific TCRs transduce thymic selection signals with the result that thymic selection is strictly MHC-specific. However, genetic deletion of both CD4

and CD8 coreceptors makes Lck freely available to all TCRs, so that TCRs that bind to any ligand in the thymus can transduce selection signals and be expressed on mature T cells in the periphery. Consequently, deletion of both CD4 and CD8 coreceptors allows the generation of mature T cells expressing MHC-independent TCRs with antibody-like recognition specificities. According to this perspective, the TCR repertoire is intrinsically diverse with specificity for both native and MHC-dependent ligands. However, MHC restriction is imposed on this diverse TCR repertoire by CD4 and CD8 coreceptors during thymic selection because of their dual specificity for intracellular Lck and extracellular MHC.