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T cell receptor specificity for major histocompatibility complex proteins

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Abstract

The ligands for $\alpha\beta$ T cell receptors are usually major histocompatibility complex proteins (MHC) bound to peptides. Although there is evidence that T cell receptor variable regions have been selected evolutionarily to bind MHC, the rules governing this interaction have not previously been apparent. However, recent solved structures of T cell receptors with related variable regions bound to MHC plus peptides suggest that some amino acids in variable region CDR1 and CDR2s almost always react in a consistent way with MHC. These amino acids may therefore have been selected evolutionarily to predispose T cell receptors towards recognition of MHC ligands.

Introduction

Proteins have been evolutionarily selected to react specifically with particular targets, other proteins, nucleic acids, substrates for enzymes and so on. This phenomenon is not difficult to understand for most proteins, which have well defined sequences and a relatively small collection of ligands which are usually created directly or indirectly by the genome of their host. However, the phenomenon is more complicated for the antigen-recognizing proteins of the specific immune system, which are germ line encoded, have related and very variable sequences but a huge range of unpredictable ligands which are not encoded by their host. For antibody proteins, the explanation is quite straightforward, variability created during the assembly of immunoglobulin genes coupled with selection by antigen and somatic mutation during response picks out antibody proteins that can bind virtually any antigen. The situation for alpha beta T cell receptors ($\alpha\beta$ TCRs) is less easily understood. Variability is created only during gene rearrangement, not somatic mutation, and the repertoire of $\alpha\beta$ TCRs on mature T cells is tremendously biased toward recognition of antigens in the form of peptides bound to major histocompatibility complex (MHC) proteins.

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How is this bias created? There are two explanations. One possibility is that the specificities of $\alpha\beta$ TCRs, like those of immunoglobulins, are intrinsically random. T cell receptors could react with any ligand. However, in order to turn into mature T cells, developing thymocytes must react with MHC/peptides in the thymus. Thus the bias for MHC reactivity on mature T cells could be caused entirely by positive selection from pool of random TCRs. Plenty of proteins are expressed on thymus cortical epithelial selected for reaction with MHC? Perhaps positive selection requires coengagement of CD4 or CD8 [1,2], and these proteins react with MHC, not other proteins on thymus epithelial cells. Alternatively thymocytes may be selected by reaction with all the other proteins on cortical epithelial cells, but then all those with high avidity/affinity are deleted by negative selection. In this case some mature T cells should bear $\alpha\beta$ TCRs with low affinity for proteins such as ICAM1. These T cells will be invisible because they will never encounter a peripheral variant of their target ligand for which they have high affinity. However, to some extent a test of this idea has been performed, searching for T cells specific for the MHC-related protein, DM, and such cells were not found [3].

Finally, $\alpha\beta$ TCRs may react with MHC because they have a builtin affinity for these proteins [4]. If such exists, then probably it will operate via the CDR1 and 2 sequences of the TCR α and β chains since these are germ line encoded, and since, in the solved structures of TCRs bound to MHC, these portions of the TCR contact MHC helix [519]. Against this idea is the fact that every species contains many TCR α and β variable regions and, although these fall into families, there is no close resemblance between the different groups [20]. Also, until recently, the solved structures of TCRs bound to MHC/peptide have failed to reveal any pattern whereby particular V region amino acids contact MHC in a reproducible way [519]. In favor of the idea is the fact that the TCR V region sequences are relatively conserved from man to mouse [20,21], indicating functions for the various V families, and the fact that TCRs nearly always engage MHC (see above) or that some conserved feature of TCRs and MHC drives the phenomenon.

With the increasing numbers of solved structures of TCRs bound to MHC, evidence for conserved interactions is accumulating.

If TCR V regions are evolutionarily designed to react with MHC, why isn't the nature of the design more evident from the solved structures of TCRs bound to MHC?

Probably there are several reasons why the evolutionarily selected rules, if they exist, have been hard to detect. First, both mouse and man, the two species from which all solved structures of TCR/MHC/peptide have been derived, code for many TCR V α s and V β s [20], and, particularly for V α , there are not a lot of structures that include the same V regions. If we assume that different V regions have been evolutionarily selected to react with MHC in different ways, the lack, until recently, of sufficient numbers of structures with any one V region has prevented discovery of patterns of reaction.

Secondly, the criteria used to look for conserved interactions may have been too strict. TCRs may be designed to bind MHC, but also have to cope with varying lengths and sequences in their nongermline encoded CDR3 regions, and in the peptides bound to MHC. These variations may force TCRs to adopt slightly different binding angles on their ligands and, in extreme cases, lift the TCR completely away from the MHC. Thus be involved in the binding, but engage slightly different sites on MHC at different angles.

Thirdly, many of the more recent structures of TCRs bound to MHC have involved unusual combinations, for example, alloreactive or autoreactive TCRs or tumor specific TCRs bound to their ligands [17,19,23,24], or TCR bound to unusually bulging peptides [25]. By their very nature such combinations may not illustrate the built-in rules very well. One could argue that what is needed at this point is solution of a lot of the conceptually more boring structures, or normal, run-of-the-mill TCRs bound to self MHC and foreign peptides, the targets that TCRs have been evolutionarily and positively selected to deal with.

Finally, and crucially, we have proposed that the evolutionarily selected rules governing TCR/MHC interaction are obscured by negative selection in the thymus [2629]. Thymocytes bearing TCRs that display their built-in ability to react with MHC too well will engage MHC with high affinity and will therefore be deleted in the thymus. T cells will only escape negative selection if their CDR3 regions modulate their ability to react with MHC sufficiently to allow the cell to be positively but not negatively selected.

A series of papers studying the reactivities of T cells from mice in which negative selection is limited supports this idea [3033]. In every case, limited negative selection allowed the appearance of mature T cells able to cross react exuberantly between MHC of different alleles and, sometimes, of different classes. Recent experiments from our that they had about the same kinetics of binding and affinities for, their ligands as normal TCRs do. However, predictably from their crossreactivity, these TCRs were much more forgiving of changes in the side chains of their MHC and peptide ligands. This result, combined with the affinity data, suggests that these TCRs that have gone through limited negative selection might be using, to a much greater extent than normal TCRs, built-in abilities to react with conserved targets on MHC.

If evolutionarily selected rules govern V region engagement with MHC, what are they?

In the last couple of years a number of TCR/MHC/peptide structures have been reported in which the TCRs use the same or related V regions [17,19,34]. This has allowed investigators to search for conserved interactions between V region CDRs and MHC. In the first analysis of this type, Maynard et al. solved the structure of a mouse TCR, 172.10, bound to its ligand, IA^u plus a peptide from myelin basic protein [17]. 172.10 uses V α 2.3 and V β 8.2, these are similar or identical to, those used by another TCR, D10, whose structure bound to its ligand, IA^k plus a conalbumin peptide, had previously been solved [8]. The authors observed that the V β 8.2 CDR 1 and 2 regions docked onto MHC almost identically in the 2 structures using, in particular, N29 β , Y46 β , Y48 β and E54 β to bind the same sites on IA^u and IA^k (the V region numbering system used here is that proposed by Arden et al. [35]). The notion that these and other V β amino acids bind in consistent ways to MHC was reinforced in a second paper from the same group, which compared the structures of TCRs all of which included mouse V β 8.2, a related mouse V β , 8.1, or their close relative in human, V β 3.1, bound to their MHCI or MHCII ligands. Again, Y46 β and Y48 β almost always bound MHC. From structure to structure these two tyrosines changed their orientation on MHC, accommodating the requirements of the TCR CDR3s, the V α region and the peptide but nevertheless they were always in about the same location.

Recently we have analyzed all the published structures of TCR/MHC/peptide complexes, together with 3 structures from our own laboratory [34,36]. Our results agree with, and extend, the conclusions of the Garcia group. Certain residues of TCR V regions do bind at approximately consistent sites on MHC. The orientation and exact location of these TCR residues as they bind MHC is not exactly the same from structure to structure. The V region residues involved vary from one V region family to another. Thus, not all human and mouse

Vβs have Y at position 48. In those Vβs that lack Y48 another amino acid may step in to fulfill the same role. For example, in some of the solved TCR/MHC/peptide structures that lack VβY48, an R at the same position binds MHC instead.

Our analysis suggested three other points. First, we found Vα amino acids that were also often used to engage MHC. Secondly, the MHC-binding Vα and Vβ amino acids and their targets on MHC are arranged such that they would require the frequently observed diagonal mode of docking of TCRs on MHC. Lastly, the V region amino acids that bind MHC consistently engage MHC at sites on the upper surface of MHC's alpha helices that are relatively exposed. The presence of MHC amino acids with small side chains allows the TCR amino acids to move within the site, from one structure to another. It seems that these regions of MHC are designed to accommodate the shifts and tilts in alignment of TCRs on MHC that are required by the variability in CDR3 and peptide sequences.

What about autoreactive and other unusual TCR/MHC interactions?

One might predict that autoreactive TCRs and their close relatives, specific for tumor antigens, that have survived the rigors of negative selection, would react with MHC and peptide in odd ways. Such TCRs may fail to use the evolutionarily conserved rules. This idea turns out to be only partially true. For example, some of the TCRs used in the analyses that found conserved interactions by the Garcia group are autoreactive, binding IA^u plus a myelin basic protein peptide. Nevertheless these TCRs seem to display the rules as clearly as any others [17,19]. On the other hand, as the Wucherpfennig [23] and Mariuzza [24] groups have pointed out, 2 autoreactive TCRs definitely bind their ligands in unusual ways, with their major interaction sites shifted towards the N terminal end of the MHC-bound peptide and a similar, but not so pronounced, shift is seen for a TCR binding a tumor antigen. Perhaps this means that, in the thymus, joint expression of CD4 and CD8 and their lock on MHC, prevents the TCRs on immature thymocytes from binding MHC in this unusual position, thus the thymocyte bearing this TCR is not deleted. In the periphery perhaps the lock imposed by, in these cases, CD4, is less severe, and now the TCR can shift along the Antigen specific receptors on T cells are constrained in many ways, by the ability of the host genome to code for them, by positive and negative selection, and by the requirement that at least most of them must be able to react with MHC proteins. It has long been believed that this last property is imposed on them not only by positive selection, but also by the fact that the variable regions of T cell receptors have been designed to react with MHCs. However, until recently there has been little experimental evidence to support this notion. With the increasing numbers of solved structures of T cell receptors bound to their MHC/peptide ligands, evidence that T cell receptor variable regions have been evolutionarily selected to react with MHC is accumulating. Certain amino acids in the CDR1 and 2s of T cell receptor variable regions are often used to bind MHC, and often bind MHC in about the same way.

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press. This paper analyzes the known structures of TCRs bound to their ligands looking for TCR amino acids that are consistently involved in reaction with MHC.

Figure 1. Negative selection removes from the mature T cell repertoire TCRs that bind MHC very well.