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What does the T-cell receptor recognize when it docks on an MHC-encoded restricting element?

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Abstract

The postulate is analyzed that single V-gene segments encode recognition of the allele-specific determinants (*a*) required for the restrictive response of the $\alpha\beta$ TCR to peptide. The consequence of this is that the positively selected V-domain, $V\alpha$ or $V\beta$, engages an allele-specific determinant (*a*) on one subunit or domain of the MHC-encoded restricting element. The entrained V-domain docks on an invariant determinant (*i*) on the complementing subunit or domain. Consequently, each functional V-domain expresses an anti-*a* site and an anti-*i* site, and all subunits or domains of MHC-encoded restricting elements express an *a*- and *i*-determinant.

The evidence, both biological and structural, discussed here strongly support this postulate which has far reaching consequences.

The goal of this commentary is to analyze the data that are necessary and sufficient to establish a postulate of the Tritope Model, namely that the V-gene segments, $V\alpha$ and $V\beta$, act as a single pool specifying recognition of the allele-specific determinants expressed on the MHC-encoded restricting elements of the species. Aspects of this postulate will also be discussed.

This version was revised to incorporate the criticisms of reviewers who also requested that I discuss additional data. As a compromise, those data which are believed to be incompatible with my argument, are analyzed.

Background

The fact to be explained is that the recognition of peptide (P) is a signal via the TCR only when it is coordinated with the recognition of a given allele of the MHC-encoded restricting element. The combining site for allele-specific recognition by the TCR is *per force* germline-selected as an individual has no way of knowing what are the alleles of the species. The combining site for the recognition of peptide is *per force* somatically generated as germline-selection is too slow to keep pace with the ability of protein targets on pathogens to escape recognition. The biology of the system tells us then that the germline-encoded V-regions of the TCR specify recognition of the allele-specific determinants (*a*) and the somatically-generated junctional regions specify recognition of peptide (Cohn, 2003; Langman and Cohn, 1999). The term "recognition" implies an interaction contributing to a signaling consequence.

The allele-specific determinants are, in the last analysis, assayed by their recognition by the V-regions of the TCR. The alleles defined by restrictive or allo-reactivity are the same,

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confirming that peptide does not act as a specificity element in defining the allele. The fact that a given allele-specific determinant on different genes may be distinguished by sequence is a second order issue referred to as degeneracy. It is the restrictive and allo-recognition by the TCR that defines the allele as a functional component in the signaling mechanism.

As predicted from the biology (Cohn, 2003; Cohn, 2005; Cohn, 2007; Langman and Cohn, 1999), single V-domains, $V\alpha$ or $V\beta$ specify the recognition of the allele-specific determinants. The structural investigations from several laboratories confirm this prediction, in particular, a recent investigation (Feng et al., 2007) in which the previous structural studies were reviewed. In addition, these investigations showed that $V\alpha$ always docks on the $A\beta$, $E\beta$ subunits of Class II MHC and the $\alpha 2$ domains of Class I MHC, K and D, whereas $V\beta$ always docks on $A\alpha$, $E\alpha$ subunits of Class II MHC and the $\alpha 1$ domains of Class I MHC, K and D.

The consequence of this is that the total number of restricting allele-specific determinants of the species must be less than the number of functional V-genes, $V\alpha + V\beta$, acting as a single pool (Cohn, 2008b; Langman and Cohn, 1999). In mouse, there are roughly 80 $V\alpha$ and 20 $V\beta$ gene-segments, a proportion of which are nonfunctional or redundant (i.e., ≥ 2 distinguishable V domains that recognize the same allele-specific determinant). The total number of allele-specific determinants functional in the murine species is less than 100, probably closer to 50.

Positive selection determines which of the restriction specificities that an individual will express. This implies two interactions. One of the V-domains must recognize a host allele-specific determinant thus posing the question, with what does the entrained V interact? Stated more illustratively, if $V\alpha$ interacts with the allele-specific determinant (a) on $A\beta$, with what on $A\alpha$ does the family of $V\beta$ s that are entrained interact?

One suggestion (Cohn, 2005; Langman and Cohn, 1999) is that the entrained V-domains dock on a determinant (i) common to Class I MHC or Class II MHC. For example, if a given $V\alpha$ is positively selected because it recognizes the a -determinant on one subunit or domain of an MHC-molecule, then the family of entrained $V\beta$ s will dock *in trans* on the i -determinant of the associated subunit or domain.

It is ruled out that in a given interaction of the TCR with an MHC-molecule, each of the V-domains docks on an allele-specific determinant as this would limit the recognition of the given MHC-molecule to a unique $V\alpha V\beta$ pair and this is not observed. In most cases, a given positively selected V is associated with a family of complemented or entrained Vs. Further, if true, alloreactivity to the alleles would be absent in the individual and that too is not found. Most reasonable, then, is that an a -site and an i -site be postulated (Cohn, 2003; Cohn, 2005; Langman and Cohn, 1999).

The Data

Let's begin by considering the Feng et al. (2007) investigation. Four TCRs were analyzed. Three are specific for A^u -Pmbp (1934.4, cl19, 172.10) and one is specific for A^k -Pcon (D10). All 4 TCRs use the $V\beta 8.2$ domain. The three specific for A^u -Pmbp use $V\alpha 4.1$ or $V\alpha 2.3$, whereas the D10 TCR specific for A^k -Pcon uses $V\alpha 2$.

Feng et al. (2007) conclude that $V\beta 8.2$ displays a conserved recognition motif ("*interaction codon*") in that it assumes a "*footprint*" over A^u_α that is identical to that of D10 TCR over A^k_α . The question then is whether $V\beta 8.2$ is interacting with an allele-specific determinant (a) or a class specific invariant determinant (i). This requires that we examine the biology of the interaction.

The biological study

The D10 TCR specific for A^k-Pcon has been extensively characterized (Table I) by analyzing the response of a hybridoma to various complemented pairs of A α and A β alleles (Hong et al., 1992; Portoles et al., 1989). The D10 TCR is restricted to A^k and alloreactive among others to the allele A^b. The D10 TCR does not appear to recognize A^u either as an allo or restricted target (Portoles et al., 1989).

In detail (Table I), lines 1 and 2 illustrate restrictive reactivity to A^k which is Pcon-dependent and alloreactivity to A^b β which is Pcon-independent. Lines 2 and 3 show us that alloreactivity is unrestricted and determined by V α 2 recognition of the allele A^b β . Line 4 confirms this, as no response is evoked when the allele A^b α is presented to V β 8.2 which sees A^k α , not, A^b α , and A^k β is presented to V α 2 which sees A^b β , not A^k β . Line 5 is particularly interesting because it shows that amino acid replacements in A^k β have either no effect on or destroy restrictive reactivity. As the allele-specific determinant on A^k β is not recognized by V α 2, it is implied that these replacements are affecting the *i*-determinant on A^k β . Line 6 is symmetrical; amino acid replacements in A^k α recognized by V β 8.2 have either no effect or leave restrictive reactivity intact. Implied, then, is that these replacements are affecting the *a*-site on A^k α . Line 7 confirms that V α 2 is specific for the A^b β allele responsible for alloreactivity as amino acid replacements either leave alloreactivity intact or destroy it. Line 8 suggests that the D10 TCR does not recognize A^u either restrictively or alloreactively.

The conclusions from these studies (Hong et al., 1992; Portoles et al., 1989) are: 1 - Single V-domains recognize allele-specific determinants either restrictively (P-dependent) or alloreactively (P-independent).

2 - V β 8.2 recognizes the allele-specific determinant on A^k α , whereas V α 2 recognizes the alloallele-specific determinant on A^b β . In addition V α 2 and V β 8.2 also recognize *i*-determinants on A β and A α respectively. When presented with A^k α A^k β (line 1), V α 2 docks on the *i*-site of A β whereas V β 8.2 docks on the *a*-site on A^k α . When D10 TCR docks on A^b α A^b β (line 3), V β 8.2 docks on an *i*-site on A^b α and V α 2 docks on an *a*-site on A^b β .

These data show that both of the V-domains in a TCR cannot dock on allele-specific determinants and be positively selected. Positive selection operates on a single V interacting with an allele-specific determinant. This positively selected V (in the D10 TCR this is V β 8.2 interacting with A^k α entrains the complementing family of V-domains (one of which is V α 2) that docks on an *i*-determinant on the complementing subunit (in this case A^k β). Alloreactivity shows that V α 2 is specific for the allele-specific determinant on A^b β that is absent in the H-2^k mouse. Docking of V α 2 on A^k β requires, therefore, an *i*-site. There are then two combining sites on each V-domain, one specific for an *a*-determinant, the other for an *i*-determinant on the MHC-encoded restricting element (Cohn, 2003; Langman and Cohn, 1999). Each subunit or domain of the MHC-molecule expresses an *a*-site and an *i*-site with which the TCR can interact. In an interaction between the TCR and the MHC-molecule, the anti-*a* and anti-*i* sites can only be engaged *in trans*.

In the A^u expressing mouse, the V β 8.2 of the TCRs anti-A^u-Pmbp does not appear to have an allele-specific ligand but this observation is misleading. The evidence that V β 8.2 recognizes

the A_{α}^k -allele and not A_{α}^u rests on the finding that the D10 TCR does not respond to A^u following either allo- or restrictive recognition (Table I, line 8) (Portoles et al., 1989). The assay is adequate for alloreactivity but questionable for restrictive reactivity because Pcon might not be properly presented to the D10 TCR by A^u .

The structural study

Feng et al. (2007) draw the conclusion from their own structural study coupled to those of Maynard et al (Maynard et al., 2005) and Reinherz et al. (Reinherz et al., 1999) that there is a unique site on A_{α} that is used to dock $V\beta 8.2$ whether it is present in a TCR that is specific for A^k -Pcon or A^u -Pmbp. Given the above cited limitation to the biological study, it can be concluded that $V\beta 8.2$ must recognize an allele-specific mimotope shared by A_{α}^k and A_{α}^u . The restriction specificity of the four TCRs is determined by $V\beta 8.2$ (i.e., allorestriction) and the "interaction codon" is an a -determinant recognized by the $V\beta 8.2$ anti- a site in all four clones.

If, in fact, $V\beta 8.2$ does dock on an a -site (the same "interaction codon") in both TCRs, A^k - or A^u -restricted, then A^k and A^u must share an allele-specific mimotope present on the A_{α} -subunits. The failure to detect restriction to A^u (Portoles et al., 1989) is, as discussed above, uninterpretable. In support of the "interaction codon" being an a -site is the finding that there is strong bias towards the use of $V\beta 8.2$ by T-cells responding to A^u -Pmbp (Acha-Orbea et al., 1988; Urban et al., 1988). This suggests that $V\beta 8.2$ is the V-domain positively selected to recognize the a -site on A_{α}^u . Consequently, the structurally defined "interaction codon" is an a -site common to A_{α}^k and A_{α}^u .

What is the meaning of "interaction codon?"

As Feng et al. (2007) were unaware of the existence of the Tritope Model (Cohn, 2003; Cohn, 2005; Cohn, 2007; Cohn, 2008b; Langman and Cohn, 1999), the fact that they come to similar conclusions based on structural arguments is, therefore, very reassuring. However, the remark that *"immunological observations give credence to the idea of a 'primordial' affinity between TCR and MHC driven by conserved sets of germline-encoded elements, which are then modulated by the MHC-bound peptide"* illustrates how deeply entrenched in their thinking is the Standard (or interaction antigen) Model (Langman and Cohn, 1999) that paradoxically their data clearly contradicts.

The phenomenon we are trying to explain is the allele-specific (restrictive) recognition of the MHC-molecule as a prerequisite for the specific recognition of peptide. Apparently, it is now agreed that single V domains recognize allele-specific determinants. This interaction defines an a -site on the restricting element and an anti- a site on the TCR. If one V-domain docks on the a -site, the complementing V-domain in that TCR would be expected to dock *in trans* on an i -site common to all or most of the alleles of a given MHC-molecule, Class I or Class II, (Cohn, 2005; Langman and Cohn, 1999). The term "interaction codon" is ambiguous with respect to the a or i interaction, and understandably so, as alleles are determined by genetics and defined by the TCR. In any case, it is to be expected that further studies of the molecular morphology of "interaction codons" will divide them into a -sites and i -sites making the term gratuitous.

As discussed previously, the requirement that an a -site be recognized in order to permit an anti-P signal (restrictive recognition of peptide) and that TCR binding to an i -site is required for functional docking, implies two signaling orientations. For a given TCR, one signaling orientation is positively selected to mediate restrictive recognition; the other is entrained and mediates alloreactivity. The family of TCRs restricted to a given MHC-molecule can, in most cases, be divided into two groups, one of which is restricted by V_{α} and entrains V_{β} which

determines alloreactivity; the other is the converse, $V\beta$ restricts and the entrained $V\alpha$ determines alloreactivity. This explains the failure of Portoles et al. (1989) to observe alloreactivity by D10 TCR for A^u . The Tritope Model faces the problem of a requirement for recognition of an a -site in order to signal from either of the two orientations (Cohn, 2003; Cohn, 2004; Cohn, 2005; Cohn, 2007; Cohn, 2008b; Langman and Cohn, 1999).

There is one point not discussed previously that might be raised here. The positioning of a - and i -sites on the MHC-molecule might introduce a nonrandomness into $V\alpha V\beta$ pairing by limiting the successful docking on a restricting element to varying extents dependent on the allele involved. For example, at one extreme there is the limited use of entrained V -genes in response to A^u -Pmbp. The positively selected $V\beta 8.2$ is complemented with either $V\alpha 4.2$ or 2.3 (Urban et al., 1988). At another extreme, in response to K^b -Pgly, the positively selected $V\beta 10$ is complemented with over 10 different entrained $V\alpha$ s (Turner et al., 1996).

While the conclusions arrived at here can be derived from the two investigations (Feng et al., 2007; Hong et al., 1992) as necessary and sufficient, very illustrative confirmation comes from another study (Felix et al., 2007).

The key to a discussion of this investigation requires a distinction between allorestriction and alloreactivity. It is essential to keep in mind that the genetic designation of the MHC-haplotype inaccurately reflects its composition. In order to discuss restrictive recognition, we must focus on the alleles of the specific genes or gene-segments in the MHC that encode the Class II subunits or the Class I domains of restricting elements. Different MHC-haplotypes can share identical genes, or different genes in a given or different MHC-haplotype can share allele-specific determinants. Further, some of the genes encoding the subunits or domains of restricting elements can be monomorphic, some highly polymorphic, with all degrees of allomorphy in between. Limiting our analysis to the murine $\alpha\beta$ TCR, we need consider, for this discussion, only the Class II subunits $A\alpha$, $A\beta$, $E\alpha$, $E\beta$ and the Class I K -, D - and L -structures, each of which has 2 domains, ($\alpha 1$ and $\alpha 2$). An allele-specific determinant is associated with each of these subunits/domains in any given MHC-haplotype.

Allorestriction occurs when the TCR interacts with an allele-specific determinant shared by two distinguished MHC-haplotypes. In essence the TCR is restrictively recognizing the MHC-molecule in both haplotypes meaning that it is both peptide- and allele-specific. This was illustrated by the Feng et al. (2007) study. The TCRs using $V\beta 8.2$ recognize in a peptide-dependent manner A_{α}^k -Pcon and A_{α}^u -Pmba because A_{α}^k and A_{α}^u share an allele-specific determinant.

Alloreactivity occurs when the TCR interacts with an allele-specific determinant not shared by the syngeneic MHC-haplotype and the allo-MHC-haplotype. This was illustrated by the Hong et al. (1992) study. $V\alpha 2$ in the D10 TCR recognizes in a peptide-independent manner the A_{β}^b allele-specific determinant that is absent on A_{β}^k . The D10 TCR is restricted to A_{α}^k via $V\beta 8.2$ and alloreactive to A_{β}^b via $V\alpha 2$.

This distinction explains the findings of Felix et al. (2007) as discussed in detail elsewhere (Cohn, 2008a; Cohn, 2008b). In their investigation, a selected set of hybridomas restricted to A^b were shown to respond to E^k in a peptide-dependent manner implying that A^b and E^k share an allele-specific determinant (allorestriction). In essence allorestriction and synrestriction are identical. The test of this in the Tritope framework would be to demonstrate that the allorestricted TCRs are positively selected by both A^b and E^k . If alloreactivity were operative the TCR would be positively selected by A^b and negatively selected by E^k .

On the role of Molecular Morphology

A major contribution to our understanding of the interactions of the TCR with its ligand, is owed to structural studies. Nevertheless in the absence of a consideration of the biology the interpretations of the interactions are limited. This is illustrated here by coupling a structural study (Feng et al., 2007) to a biological study (Hong et al., 1992).

The structural studies are being uniformly interpreted in terms of the Standard Model. This framework owed to Matzinger and Bevan (Matzinger and Bevan, 1977) has driven an enormous amount of crucial experimental work and has been reformulated by Colf et al. (Colf et al., 2007) who view "alloreactivity" as equivalent to "crossreactivity." They conclude "that alloreactions are not only due to molecular mimicry but they are also a consequence of less predictable interactions with alloantigens that have more significant structural diversity than syngeneic MHC." Since what is allogeneic for one member of a species is syngeneic for another, it is hard to rationalize this conclusion. They view alloreactivity as functioning on a sliding scale between "peptide-centric" and "MHC-centric."

In the Tritope framework peptide does not play a role as a specificity element in alloreactivity (as distinct from allorestriction). The recognition of peptide by the anti-peptide (P) site on the TCR is not required in order to signal the T-cell. The signaling trigger is a specific interaction with the alloallele-specific determinant as necessary and sufficient.

The limitation to molecular morphology lies in the lack of a general rule that permits one to translate relationships in space into events in time. Not every "interaction" defined by proximity or other (van der Waals forces, hydrogen bonding, electrostatic forces, etc.) specifically contributes to signaling. Particularly in the case of the hypervariable junctional regions of the α and β subunits, some of the interactions with ligand are fortuitous. Predictably, using a large enough sample, if one looked at the distribution of structurally defined interactions with peptides in the alloreactive configuration, it would be similar to that of restrictive interactions where the peptides are non-signaling. In the Tritope framework, to describe the interaction of TCR with its ligand on a sliding scale between peptide- and MHC-centric has no heuristic value as restrictive recognition requires specific defined interactions with both peptide and MHC.

While for restrictive reactivity (signaling) the cooperative interactions between TCR and ligand might be contributed to differentially (affinity) by the peptide—anti-P and the MHC—anti-MHC interactions, both are obligatory. For alloreactivity (signaling) viewed in the Tritope framework, only an interaction with allo-MHC is obligatory; peptide is acting as a structural element complexed to the MHC-molecule and necessary for its expression and conformation, not as a specificity element recognized by the TCR anti-P as signaling.

Just a thought!

Popper tells us that a good theory incorporates the experiments that lead to its demise. Theories are there to fail. While every paper describing the Tritope Model (Cohn, 2003; Cohn, 2004; Cohn, 2005; Cohn, 2008a; Cohn, 2008b) has included such critical experiments, the community of supporters of the Standard, Interaction or Slip and Slide Centric Model have yet to face this requirement.

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List of abbreviations

TCR, T-cell receptor restrictively recognizing peptide; MHC, Major Histocompatibility Complex; *i*, an invariant or common site on allelically distinguished MHC-molecules; *a*, an

allele-specific site on the MHC-molecule; Pcon, conalbumin peptide; Pmbp, myelin basic protein peptide; Pgly, a peptide from the glycoprotein of herpes simplex virus.

Table I
The relationship between alleles of RII A subunits and their recognition by the V-regions of the D10 TCR

Alleles of subunits		Response of D10 in presence (Con ⁺) or absence (Con ⁻) of the conalbumin peptide	
Aα (Vβ8.2)	Aβ(Vα2)	Con ⁺	Con ⁻
1. k	k	+	-
2. k	b	+	+
3. b	b	+	+
4. b	k	-	-
5. k	k mutant (k→d)	+	-
6. k mutant (k→d)	k	-	-
7. b	b mutant (b→k)	-	-
8. u	u	+	+
		-	-

Data extracted from Portoles et al (Portoles et al., 1989) and Hong et al (Hong et al., 1992).

(Vβ8.2) or (Vα2) = the V region interactive with the given A subunit.

k→d, b→k = amino acid replacements of one subunit that are present in the allele.