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The Tritope Model for restrictive recognition of antigen by T-cells II. Implications for ontogeny, evolution and physiology☆

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Abstract

Based on the *Tritope Model* of the TCR [Cohn, M., 2005c. The Tritope Model for restrictive recognition of antigen by T-cells. I. What assumptions about structure are needed to explain function? Mol. Immunol. 42, 1419–1443], a set of functional and evolutionary problems surrounding restrictive recognition of antigen are discussed. These include the origin of allele-specific recognition, the selection pressures for polygeneism and polymorphism, the TCR signaling interactions, the centrality of effector T-helper (eTh)-dependence for activation, the role of haplotype exclusion, "nonclassical" MHC-elements, alloreactivity versus xenoreactivity, etc. Further, a set of observations believed to support the *Standard Model* are reinterpreted.

Keywords: TCR; Restrictive recognition; Signaling mechanism; Alloreactivity; Positive and negative selection; Repertoire; MHC polymorphism; Self-nonself discrimination

A previous paper (Cohn, 2005c) detailed a new model (referred to as the *Tritope Model*) of the T-cell antigen-receptor (TCR) and analyzed its effectiveness in dealing with three basic phenomena, restrictive recognition, positive selection and allorecognition. The reasons for developing a model competing with the *Standard Model* have been discussed (Cohn, 2003, 2004a,b, 2006a; Langman and Cohn, 1999). Here we will extend the analysis of the Tritope Model by considering a set of phenomena related to the genetics, ontogeny and evolution of the TCR–MHC system. Further, the steps in the Self (S)–Nonself (NS) discrimination that are affected by the Tritope Model will be analyzed.

1. Recalling the Tritope Model (Cohn,2005c)

The TCR encodes two distinctly different repertoires. One is germline-selected to recognize the allele-specific determinants (a) on the MHC-encoded restricting elements (R) of the species; the other is a somatically generated random repertoire that recognizes peptide (P) bound to the restricting element (R) as [PR].

In order to map the two repertoires onto the TCR structure it was argued that (see List of Abbreviations):

1. Single V-gene segments, Vα or Vβ, encode recognition of the allele-specific determinants (*a*).
2. Each domain (RI) or subunit (RII) of the R-element expresses an allele-specific determinant (*a*) (i.e., 2*a* per R).

Abbreviations: MHC, major histocompatibility complex; R, MHC-encoded restricting element; P, peptide; Ps, self-peptide; Pns, Nonself-peptide; R_T, the restricting element mediating positive selection in thymus; TCR, T-cell antigen-receptor; Ig, immunoglobulin; R_A, allo-R, Nonself alleles of R; RI, class I restricting element; RII, class II restricting element; V_T, variable region of the TCR; C_T, constant region of the TCR; S, Self; NS, Nonself; a, allele-specific epitope on R; i, invariant epitope on R; c–a, combining site (c) on V_T for a; c–i, combining site (c) on V_T for i; Vα, the variable domain encoded in the Tα-locus; Vβ, the variable domain encoded in the Tβ-locus; oT, T-cell prior to positive selection ($CD8^+CD4^+$); iT, T-cell after positive selection; eT, effector T-cell; eTc, cytotoxic effector T-cell; eTh, effector helper T-cell; anti-R, c–a plus c–i recognition of R; d, number of allele-specific determinants (a) per R; Tα, the gene locus encoding the α-subunit of the TCR; Tβ, the gene locus encoding the β-subunit of the TCR; CMI, cell-mediated immunity

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Table 1
The cartographic description of R-elements

Domain	RI	RII
West	α2	β1
East	α1	α1

3. Peptide (P) is recognized by an anti-P site on the TCR formed by complementation of the CDR3 junctional regions of the α and β subunits.
4. The restricting specificity and its relationship to function is positively selected by the "Self" or thymic-R (R_T) dependent on recognition of one V-domain (Vα or Vβ) (Cohn, 2004a, 2005c, 2006a).
5. The unselected or entrained V-domain encodes recognition of allo-R (R_A).

The Tritope Model (Cohn, 2003, 2004a, b, 2005c; Langman and Cohn, 1999) is so named because it describes a TCR with three paratopes anti-R_T, anti-R_A and anti-P. The TCR docks on the [PR_T]-complex via two combining sites (c), one (c–a) allele-specific and the other (c–i) specific for an invariant site together referred to as "anti-R." These two combining sites (c) are distributed on the subunits of the TCR, Vα and Vβ, such that one V-subunit engages the *a* determinant and the other engages the *i* determinant *in trans* on R when the TCR docks. The reader is referred to the detailed description of the TCR–[PR] interaction (see Figs. 1 and 2 in Cohn, 2005c).

The peptide binding groove on R is formed between the two domains of Class I R (RI) or the two subunits of Class II R (RII). We refer to these domains (or subunits) as East (E) and West (W) (Table 1). The peptide is bound in the groove, N → C, such that the West domain (or subunit) anchors the N terminal portion and the East domain (or subunit), anchors the C terminal portion of the peptide. The E and W domains of R have their TCR docking determinants distributed in a geometry discussed previously (Cohn, 2003, 2005c; Langman and Cohn, 1999).

The Vα has two combining sites (c), c–aW and c–iW, whereas Vβ has two sites, c–aE and c–iE. The docking of a VαVβ pair engages *in trans* one *a* site and one *i* site on R. The TCR binds in a "fixed" docking mode, Vα always docks on the West domain (α2 of RI or β1 of RII) and Vβ always docks on the East domain (α1 of RI or α1 of RII). Within this fixed docking mode the TCR can function in one of two positively selected signaling orientations, aW → iE or aE → iW. This docking geometry allows the anti-P site to straddle P and, if complementary, engage it in a stable conformationally driven signaling interaction (referred to as Signal[1]). If not complementary, the TCR disengages.

Each VαVβ pair has its restricted or functional signaling orientation positively selected in the thymus (i.e., aW → iE or aE → iW) and an opposite unselected orientation (i.e., respectively, aE → iW or aW → iE) responsible for alloreactivity. Initiating a signal via the TCR resulting from the positively selected orientation (restrictive reactivity) requires an interaction between P and anti-P. Initiating a signal via the same TCR interacting in the unselected orientation (alloreactivity) does not require an interaction between P and anti-P. The change in geometry of the interactions with *a* and *i* from the positively selected to the unselected orientation initiates signaling by allo-R (R_A). Under this model, alloreactivity is a byproduct of evolutionary selection for restrictive reactivity; it is not directly selectable.

The existence of two signaling orientations (aW → iE or aE → iW) of the TCR–[PR] interaction requires that anti-P be born in one of two conformations, referred to as *flIp* and *flOp*, each of which upon interaction with P can initiate a signal to the T-cell. The two anti-P conformations are structurally determined prior to positive selection, one simple assumption being that the conformation, *flIp* or *flOp*, is determined by the Dβ-reading frame. Positive selection determines which conformation will be functional during restrictive recognition of antigen. The interaction of P with anti-P results in a change of conformation to an intermediate conform, Φ, that initiates signaling from either orientation, flOp or flIp. The symbol Φ is derived as a composite of the I and O in flIp and flOp. These conformational transitions are schematized in Fig. 1.

In order to make the triggering of restricted effector function, both P- and R-dependent, two events are required. One reasonable mechanism would be that the interaction of the TCR c–a site with *a* and the c–i site with *i* induces a concerted conformational change in both [PR] to reveal P (and permit coreceptor binding), and in the TCR to expose the anti-P site, which, upon interaction with P, delivers Signal[1] to the T-cell. This signal is initiated consequent to a sequence of interactions between the TCR and [PR], first [a + c–a], then [i + c–i], and last [P + anti-P]. If anti-P is not engaged by P in a signaling interaction the TCR disengages from the [PR] complex. This *a priori* view of T-cell scanning (Cohn, 2003, 2005c; Langman and Cohn, 1999) has experimental support (Wu et al., 2002).

2. The relationship between the anti-R repertoire and R-alleles

We assume that the sites on a given R-element to which the anchor residues of the peptide are bound, determine the allele-specific determinants (*a*) recognized by the TCR. Further, we assume that the peptide is anchored in sites on R determined uniquely by one or the other domains (RI) or subunits (RII). This means that each *evolutionarily selected* peptide anchoring site on R is determined by a single domain or subunit; it is not determined by complementation of domains or subunits. The simplest picture would be that the peptide is bound to R largely as a property of anchor amino acid residues at or close to the N- and C-terminal ends, thus orienting the peptide in the groove, North to South with the N-proximal residue anchored West and the C-proximal residue anchored East. As different R-alleles recognize peptides via different anchor residues, the question arises, how does evolution keep the definition of different alleles of R-elements based on the TCR recognition of allele-specific determinants acceptably concordant with the definition of different alleles of R-elements based on the sites to which anchor residues of the peptides bind? One answer would be that the site where anchor residues of the peptide are complexed to R generates the allele-specific determinant. Thus mutations in R