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Review

Gamma delta T cell receptors

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Abstract. Gamma delta ($\gamma\delta$) T cells are among the least understood components of the immune system. While these cells appear to contribute uniquely to host immune competence, defining their functions in the context of host biology and pathology has been difficult. This is largely because it is unclear what antigens the $\gamma\delta$ T cell receptor repertoire is directed against. During the past year, there have been noteworthy advances in this area. Their significance in the context of $\gamma\delta$ T cell biology is discussed.

Keywords. Gamma delta T cell receptor, gamma delta T cell receptor structure, gamma delta T cell, MHC, pyrophosphomonoester, ligand recognition.

Introduction

Adaptive immune responses are vital to the survival of vertebrate animals. They are essential for the clearance of pathogens during primary infection and for providing protection from reinfection. The key components of the adaptive immune system are the lymphocytes, which include B cells and T cells, where T cells can be further divided into $\alpha\beta$ T cells and $\gamma\delta$ T cells based on their antigen receptors.

$\gamma\delta$ T cells together with B cells and $\alpha\beta$ T cells are present in all but the most primitive vertebrate animals and these are the only types of cell that use somatic gene rearrangement to generate antigen receptors. By making use of VDJ recombination, large numbers of different receptors can be generated from limited numbers of germline V, D and J segments. The resulting repertoire of lymphocytes can specifically respond to vast numbers of pathogens. This rearrangement mechanism also generates receptors with variable affinities to a given antigen. Thus, lymphocytes expressing receptors with optimal antigen recognition abilities can selectively expand, and can be maintained during and after immune responses. This feature contributes to a host's ability to mount more rapid and more robust responses when pathogens are reencountered.

Unlike $\alpha\beta$ T cells and B cells, whose discovery was aided by their anticipated functions, $\gamma\delta$ T cells were discovered after the serendipitous isolation of the T cell receptor (TCR) γ chain gene [1]. Moreover, it is clear that while in mouse and human, all the well-defined immune responses attributed to T cells, such as killing infected cells and helping the development of antigen-specific B cells, are primarily performed by $\alpha\beta$ T cells, $\gamma\delta$ T cell-deficient mice are immune compromised. Studies with mice deficient in either $\alpha\beta$ and/or $\gamma\delta$ T cells show that there are both quantitative and qualitative differences in the way infections are cleared. In addition, abnormally high percentages of $\gamma\delta$ T cells have been reported among the infiltrating lymphocytes in the target tissues of autoimmune diseases, and patients with bacterial and viral infections often exhibit increased percentages of $\gamma\delta$ T cells in their peripheral blood [reviewed in refs. 2, 3]. These results indicate that $\gamma\delta$ T cells respond and contribute to immune defense in ways that are distinct from $\alpha\beta$ T cells, but do not clarify the nature and the molecular mechanism of $\gamma\delta$ T cell functions.

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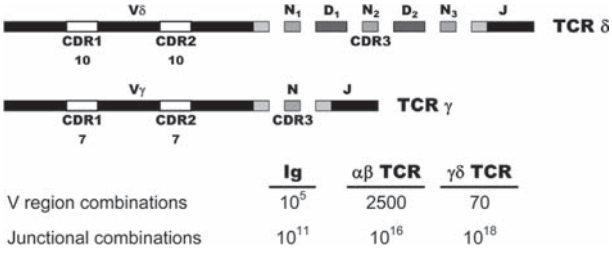
$\gamma\delta$ T cells comprise the first wave of T cells that appears during fetal thymic ontogeny. But, as the development of $\alpha\beta$ T cells progresses, their numbers increase while those of $\gamma\delta$ T cells remain stable. In adult animals, and especially in mice and humans, $\gamma\delta$ T cells make up only a small percentage (~1–5%) of spleen and lymph node T cells. These numbers are higher in ruminants and chickens. $\gamma\delta$ T cells also line the epithelial layers of various organs, such as the small intestine, liver and reproductive tract [reviewed in refs. 2, 3]. Yet, other than within the mouse skin, there is no known anatomic location of $\gamma\delta$ T cells where one cannot find $\alpha\beta$ T cells as well. Although some $\gamma\delta$ T cells may have specialized functions, such as producing tissue-specific growth factors in the mouse skin [4], most $\gamma\delta$ T cells can secrete cytokines similar to those produced by $\alpha\beta$ T cells and can mount cytolytic responses upon being triggered through the $\gamma\delta$ TCR. Significantly, gene expression profiles of $\gamma\delta$ and $\alpha\beta$ T cells that were isolated from the epithelial layer of murine small intestines indicated that both types of cell actively transcribe similar effector function genes [5]. These studies suggest that $\gamma\delta$ and $\alpha\beta$ T cells have similar effector functions and that ligand recognition may contribute significantly to the unique role of $\gamma\delta$ T cells in maintaining host immune competence.



	Ig	αβ TCR	γδ TCR
V region combinations	10^5	2500	70
Junctional combinations	10^{11}	10^{16}	10^{18}

Figure 1. Potential amino acid sequence diversities of murine immune receptors. The calculated potential amino acid sequence diversities in immunoglobulin (Ig) (without allowance for somatic hypermutation) and $\alpha\beta$ and $\gamma\delta$ TCR genes are shown. The first two hypervariable regions of Ig and TCRs (CDR1 and CDR2) are encoded within the V gene segments. The pairing of the random V gene segments (V_H and V_L, Vα and Vβ, Vγ and Vδ) generates the combinatorial diversity listed as V region combinations. The third hypervariable regions (CDR3s) are encoded within the D and the J gene segments and are listed as junctional combinations. The mechanisms for diversity generation used for this calculation include different D and J gene segment usage, N nucleotide addition of up to six nucleotides at each junction, variability in the 3′ joining position in V and J gene segments and translation of D gene segments in different reading frames. Numbers are corrected for out-of-frame joining, codon redundancy and N region mimicry of germline sequences as detailed in Elliot et al. [42]. The last few amino acids from the TCR V gene segments also contribute to CDR3 diversity, but their effects are negligible and are not included in the calculation.

$\gamma\delta$ and $\alpha\beta$ TCRs recognize different antigens

Indeed, $\gamma\delta$ and $\alpha\beta$ TCRs show different antigen recognition requirements and recognize different sets of antigens [reviewed in ref. 6]. While most $\alpha\beta$ T cells recognize processed protein antigens in the form of peptides associated with major histocompatibility genes (peptide/MHC), there is no known antigen processing and presentation requirement for ligand recognition by $\gamma\delta$ T cells and the antigens need not be peptide/MHC complexes [6]. Thus, damaged tissues, cells and pathogens can be recognized directly by $\gamma\delta$ T cells without a requirement for antigen degradation and specialized antigen-presenting cells. This should allow for greater flexibility in $\gamma\delta$ T cell responses than is found in classical $\alpha\beta$ T cell responses.

The CDR3 regions formed by VDJ recombination are the key components for antigen recognition and the TCR δ chains have the highest potential diversity in the CDR3 loop among all antigen receptor chains. In contrast, TCR γ and δ loci contain many fewer commonly used V genes than the TCR α and β and most immunoglobulin (Ig) loci (Fig. 1) [7]. Furthermore, when the CDR3 length distributions of all known antigen receptor polypeptides from mice and humans were analyzed, the CDR3 regions of Ig light chains were shown to be short and constrained in length, while those of Ig heavy chains are longer and more variable in length. For α and β TCR chains, the CDR3 length distributions are significantly constrained and are about equal, which may reflect the requirement for these chains to contact both MHC and bound peptide. In $\gamma\delta$ TCRs, the γ chain CDR3 loops are short, with narrow length distributions similar to Ig light chains, and the δ chain CDR3 loops are long with broad length distributions similar to Ig heavy chains [8]. Therefore, on the basis of the key structural components for antigen binding, $\gamma\delta$ TCRs are more similar to Ig than to $\alpha\beta$ TCRs.

A protein complex on the cell surface is a ligand for phospho-antigen-reactive human Vγ9Vδ2 T cells

The identification of $\gamma\delta$ TCR ligands has turned out to be difficult and confusing. Different ‘agents’ have been found to stimulate $\gamma\delta$ T cells, but only a few have been shown to be both necessary and sufficient to trigger $\gamma\delta$ T cells through the TCRs and are therefore qualified as $\gamma\delta$ T cell antigens. These include the MHC class Ib molecule T10 and the closely related T22 (94% amino acid identity), which has been found to be a natural ligand for 0.2–2% of $\gamma\delta$ T cells in all strains of mice [9, 10], the MHC class I-like molecules MICA and MICB [11] and the recently described ATP synthase-F1 (AS)/apolipoprotein A-1 complex [12]. In all three cases, the proteins are recognized directly.

Moreover, the same population of human $\gamma\delta$ T cells that recognizes AS/apolipoprotein A-1 complexes is also activated by a set of non-peptidic pyrophosphomonoesters that are collectively referred to as phospho-antigen (phosphoAg). These compounds are produced through

the isoprenoid biosynthetic pathway [13] and are found to stimulate large numbers of human peripheral blood $\gamma\delta$ T cells. These cells express Vγ9Vδ2 TCRs (and are commonly referred to as Vγ9Vδ2 cells) and respond to tumor cell lines, alkylamines and aminobisphosphonates *in vitro*. While the $\gamma\delta$ TCRs from some of these cells have been shown to confer reactivity, there has been no report that any of these small non-peptide ligands alone are sufficient for activating $\gamma\delta$ T cells nor have any of these compounds been shown to bind to $\gamma\delta$ TCRs. In fact, T cell activation by phosphoAg requires cell-to-cell contact [14–16], suggesting that phosphoAg stimulation occurs through cell surface molecules.

Interestingly, there is a tight correlation between β-phosphate cleavability, chemical reactivity and $\gamma\delta$ T cell bioactivity of synthetic phosphoAg derivatives [17]. These results suggest that a cell surface ectoenzyme endowed with phosphatase activity is required for the reactivity of phosphoAg. AS, which catalyzes ATP hydrolysis in addition to ATP synthesis, would be a good candidate. Although direct binding studies between AS and phosphoAg and analyses of the blocking activity of AS inhibitors on phosphoAg-induced $\gamma\delta$ T cell activation have yet to be performed, the involvement of AS in the early steps of isopentenyl pyrophosphate (IPP) biosynthesis [18] is consistent with this supposition.

The V, D and J segments at the CDR3 region of the TCR δ chain encode major antigen contact residues of T10/T22-specific $\gamma\delta$ TCRs

Another perplexity in identifying $\gamma\delta$ T cell ligands comes from observations that $\gamma\delta$ T cells from different anatomical sites show preferential V gene expression [e.g. Vγ1 and Vγ4 in the spleen and Vγ7 in the intestinal intraepithelial lymphocyte (IEL) compartment; nomenclature according to Heilig and Tonegawa, ref. 19) [3] and from reports suggesting that $\gamma\delta$ T cell functions segregate with Vγ usage [20, 21]. This has led to the suggestion that $\gamma\delta$ T cells are selected differently and that the bias in Vγ gene usage enables them to respond to antigens that are specific to their resident tissues [3, 22] despite the diverse CDR3 sequences of $\gamma\delta$ TCRs. To resolve this issue, it is essential to understand the molecular basis of $\gamma\delta$ TCR antigen recognition.

Shin et al. [23] took advantage of the fact that T22-specific $\gamma\delta$ T cells from non-immmunized mice can be identified and isolated with a tetrameric T22 staining reagent to characterize T22-specific $\gamma\delta$ TCRs at a single cell level. In the analysis was found, that the majority of T22 tetramer-positive cells expressed Vγ1 and Vγ4 in the spleen and a sizable population of these cells expressed Vγ7 in the IEL compartment. Thus, Vγ usage reflects the tissue origin of the $\gamma\delta$ T cells and does not predict antigen

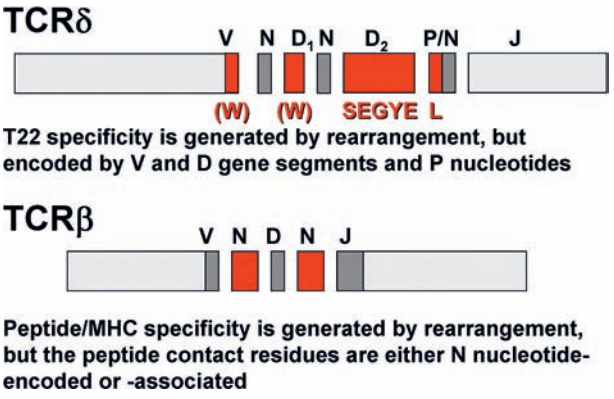


Figure 2. Generating antigen specificity. Schematic diagrams of antigen recognition determination are shown at the CDR3 regions of TCRδ from T22-specific $\gamma\delta$ TCRs and of TCRβ from peptide/MHC-specific $\alpha\beta$ TCRs. The major and minor gene segments encoding antigen recognition amino acids are labeled in red and gray, respectively. The W-(S)EGYEL motif of the T22-specific TCRδ is indicated.

specificity. Consistent with this, a recent study by Zhao et al. [24] indicates that preferential Vγ7 usage by IELs primarily results from a tissue-specific epigenetic control of Vγ7 accessibility during VJ rearrangement.

In fact, various Vγ and Vδ sequences were associated with T22-specific TCRs and no unique sequence motif was present in TCR γ chains. Instead, the only defining feature was a prominent CDR3δ sequence motif of a tryptophan (W) encoded by the Vδ or Dδ1 gene segments, and the sequence (serine)-glutamic acid-glycine-tyrosine-glutamic acid [(S)EGYE] followed by a P nucleotide-encoded leucine (L) (Fig. 2). Aside from this motif, the CDR3δ sequences were diverse and were encoded by various Vδs, N and P nucleotides and Dδ1 of different lengths and reading frames. TCR gene transfer experiments showed that TCRs that had the W-(S)EGYEL motif could bind T22 tetramers, whereas those that lacked this motif could not. Significantly, sequence variations in the CDR3 regions around this motif modulated the affinity and the kinetics of T22 binding. Indeed, the T22-specific TCR repertoire in normal mice covers a range of affinities, as is evident by the large range of T22 tetramer staining intensities [10, 23].

That the W-(S)EGYEL motif in the T10/T22-specific CDR3δ loop indeed contains the antigen contact site became evident from the structure of the G8 $\gamma\delta$ TCR and T22 co-crystal [25] – the first crystal structure of $\gamma\delta$ TCR and its ligand. T22 is similar in structure to MHC class I, but one side of the normal peptide-binding groove is severely truncated, exposing the β sheet floor [26] (Fig. 3). G8 binds T22 at an angle that results in an almost side-on interaction that is primarily mediated by the fully extended CDR3δ loop and the β sheet floor of T22, while CDR3γ makes only minor contacts (Fig. 3).

Extensive junctional sequence and length heterogeneity, particularly within CDR3δ, have also been reported

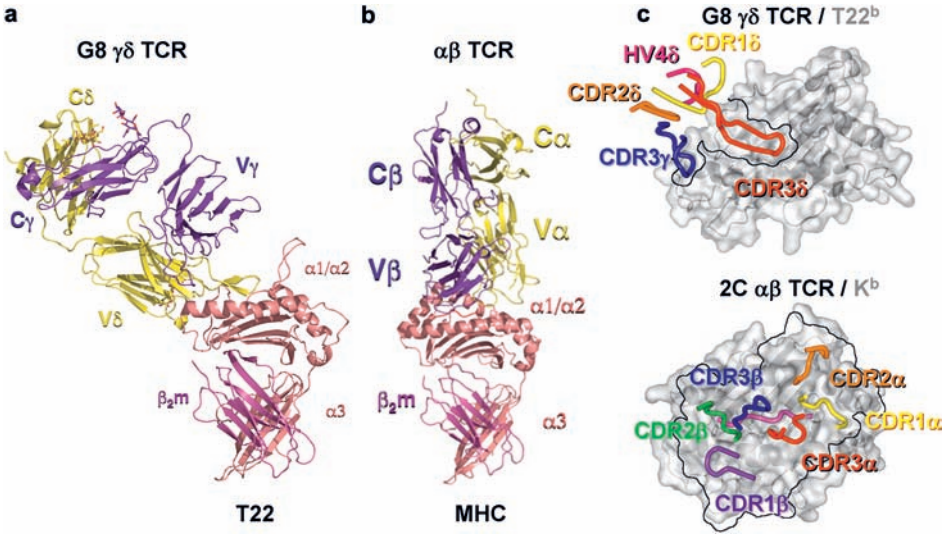


Figure 3. Antigen recognition by $\gamma\delta$ and $\alpha\beta$ TCRs. The structure of the G8 TCR bound to T22 (*a*), the structure that is commonly observed with $\alpha\beta$ TCR and peptide/MHC complexes (*b*) and the recognition footprints and locations of CDR loops of G8 $\gamma\delta$ TCR on T22 and 2C $\alpha\beta$ TCR on K^b (*c*) [adapted from ref. 25].

for the human Vγ9Vδ2 cells [26]. The majority of these TCRs uses the same Jγ element (JγP) and share a few highly recurrent CDR3δ motifs, including a small hydrophobic residue (valine, leucine or isoleucine) at position 97 of the δ chain (δ97) [27]. TCR gene transfer and site-directed mutagenesis studies have shown that the small hydrophobic motif at δ97 and two lysine residues encoded by the 5′ end of JγP are necessary for phosphoAg reactivity [28, 29]. The small hydrophobic motif is mainly encoded by N nucleotides in adult and by P nucleotides in fetal Vγ9Vδ2 T cell clones [30]. Thus, the specificities of phosphoAg-reactive and T10/T22-specific $\gamma\delta$ TCRs appear to be conferred by a limited set of 'primordial' germline or germline-like residues in the CDR3 region, with the extensive CDR3 junctional sequence diversity conferring wide ranges of ligand-binding affinity.

Although the CDR3 regions of $\gamma\delta$ TCRs, like those of $\alpha\beta$ TCRs, are important for antigen binding, the nature of the antigen recognition determinants in these $\gamma\delta$ TCRs appears to be very different from that of the majority of $\alpha\beta$ TCRs. In the case of T22-specific TCRs, the CDR3δ motif is encoded by Dδ, Vδ, and P nucleotides, whereas, in $\alpha\beta$ TCRs, the most critical residues for peptide/MHC recognition are encoded either completely or partially by N nucleotides in both CDR3α and CDR3β (Fig. 2). A T cell repertoire generated from somatic recombination but whose specificity is conferred by germline-encoded amino acids would be created at a much higher frequency than one whose specificity is conferred primarily by N nucleotide additions. Indeed, the frequency of T22-specific $\gamma\delta$ T cells in normal mice (0.1–2%) is much higher than the frequency of one in 10^5–10^6 of naive $\alpha\beta$ T cells that are specific for a given peptide/MHC complex. If $\gamma\delta$ TCR specificity for other ligands is determined in a similar manner, then the $\gamma\delta$ T cell repertoire must be directed against a relatively small number of ligands, of the order of hundreds to thousands versus tens of thousands, but with a high frequency. This could provide a solution to the apparent paucity of $\gamma\delta$ T cells and would allow a significant response without an initial need for clonal expansion as is required for most $\alpha\beta$ T cell responses.

Shaping of the $\gamma\delta$ TCR repertoire

The key roles played by enzymatic/combinatorial constraints in favoring the generation of $\gamma\delta$ TCRs with appropriate specificities is further highlighted by analyses of several murine fetal thymocyte-derived intraepithelial $\gamma\delta$ T cell subsets. Most $\gamma\delta$ T cells in murine skin and reproductive organ mucosa express identical TCRs encoded by Vγ5Jγ1/Vδ1Dδ2Jδ2 and Vγ6Jγ1/Vδ1Dδ2Jδ2 rearrangements, respectively. In TCRCδ-deficient mice, which can rearrange their TCR γ and δ genes but cannot express functional $\gamma\delta$ TCRs, the fully germline canonical junctions of the above Vγ5Vδ1 and Vγ6Vδ1 TCRs are generated at high frequency through homology-guided recombination within fetal thymocytes [31].

Beyond enzymatic/recombination constraints, upregulation of $\gamma\delta$ T cell ligands in a variety of immune/inflammatory contexts may lead to chronic stimulation and subsequent expansion of reactive $\gamma\delta$ T cell subsets early in life. Such antigen-driven expansion processes may give rise to the high frequency of phosphoAg-reactive $\gamma\delta$ T cells, which can represent up to 1–5% of the entire peripheral blood lymphocyte pool in adults [13, 31], and could explain why most of these cells display a memory phenotype

[32]. The combination of gene rearrangement constraints and antigen-driven selection may allow for the production of a large pool of $\gamma\delta$ T cells that is able to respond to self-ligands that are upregulated on stressed, infected and/or activated cells. Consistent with this, most $\gamma\delta$ T cell ligands that have been studied so far are expressed at a higher level in stressed, activated and/or transformed cells. T10/T22 expression is induced on activated lymphocytes and on infected macrophages [ref. 10, and data not shown]. Similarly, CD1c, which activates some human $\gamma\delta$ T cells in a TCR-dependent manner [33] is upregulated on activated T cells and on T cell leukemias and is highly expressed on dendritic cells [34]. MICA/B molecules, which are recognized by some human colon carcinoma-derived $\gamma\delta$ T cell clones, are expressed on heat-stressed cells and on a broad array of epithelial and hematopoietic tumors [35]. Likewise, increased surface expression of AS has been reported on a broad array of tumor cells [12, 36, 37]. Surface AS expression on endothelial cells has also been implicated in the regulation of neo-angiogenesis [38]. Along these lines, murine intraepidermal $\gamma\delta$ T cells respond to stressed or transformed keratinocytes in a TCR-dependent manner [39]. Metabolites in biosynthetic pathways such as IPP and hydroxydimethylallyl diphosphate that are tightly coupled to the bioenergetic status of mammalian cells or microbes are also known to stimulate human $\gamma\delta$ T cells [13] and IPP production is greatly upregulated in transformed cells [40]. In addition, several murine $\gamma\delta$ T cell hybridomas were found to respond to cardiolipin and to structurally related phospholipids in the presence of β2-glycoprotein-1 (apolipoprotein H) [41]. Taken together, these results suggest that $\gamma\delta$ T cells, through the recognition of different antigens, can regulate immune responses, control infections and modulate tumor development.

A self-reactive TCR repertoire with diverse ligand-binding properties would enable more flexible and efficient responses to changes in self-ligand expression when coupled with selection against high-affinity T cells that might respond inappropriately to basal ligand expression levels. Thus, $\gamma\delta$ T cells may play a unique role in a variety of immune and non-immune homeostatic processes and during pathological situations.

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