TCR Mechanobiology: Torques and Tunable Structures Linked to Early T Cell Signaling

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TCR mechanobiology: torques and tunable structures linked to early T cell signaling

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THE TCR STRUCTURE: OVERVIEW

The αβ TCR is a multimeric transmembrane complex composed of a disulphide-linked antigen binding clonotypic heterodimer in non-covalent association with the signal-transducing CD3 subunits (CD3γ, CD3δ, and CD3ζ) (reviewed in Rudolph et al., 2006; Smith-Garvin et al., 2009). TCR signaling via CD3 dimers evokes T cell lineage commitment and repertoire selection during development, maintains the peripheral T cell pool, and further differentiates naïve T cells into effector or memory cell populations upon immune stimulation. Each CD3γ, γ, and δ subunit contains an extracellular immunoglobulin (Ig)-like domain, a membrane-proximal stalk region, a transmembrane segment, and a cytoplasmic tail. The interaction between an αβ TCR heterodimer on the T cell and a pMHC ligand on an antigen-presenting cell (APC) initiates a cascade of downstream signaling events. These events are transmitted via the immunoreceptor tyrosine-based activation motif (ITAM) elements in the cytoplasmic tails of the associated CD3 subunits, whose lengths are substantial relative to those of the TCR α and β tails (Reth, 1989; Letourneur and Klausner, 1992; Acuto et al., 2008; van der Merwe and Dushek, 2011) The various CD3 chains induce distinct patterns of cellular protein tyrosine phosphorylation upon activation to recruit intracellular adaptors and signaling molecules. Early, intermediate, and late gene activation programs ensue (Crabtree and Clempstone, 1994). Reviews such as Rudolph et al. (2006) have focused on the structural nature of immune recognition involving Vα and Vβ domains of a given TCR and its pMHC ligand. How recognition of pMHC by a weakly interacting αβ TCR heterodimer on the T cell surface evokes intracellular signaling via the adjacent CD3 components of the TCR complex has remained undefined.

Functional TCR αβ heterodimers were first identified by mAbs on antigen-specific T cell clones and then T cell hybridomas (Acuto et al., 1983; Meuer et al., 1983a,b; White et al., 1983). Subsequent sequence analysis of TCRs predicted that they would share with antibodies a common structural basis of ligand recognition, akin to an antibody Fab fragment (Novotny et al., 1986; Chothia et al., 1988). These results agreed with peptide mapping studies of α and β subunits which identified conserved as well as variable peptides, implying the existence of constant and variable domains in the TCR α and β subunits. The biochemical results were later confirmed and extended by DNA cloning (Chien et al., 1984; Yanagi et al., 1984), and elegantly delineated further by the crystal structure of an intact murine αβ TCR (Garcia et al., 1996) and a complex between a human TCR, viral peptide, and human MHCI molecule that followed (Garboczi et al., 1996). Structures of TCR αβ heterodimers and antibody Fab fragments seem very similar. While each of the four TCR α and β domains, like those of Fab, has been assigned an Ig fold, deviations are notable in both TCR constant domains (Bentley et al., 1995; Garcia et al., 1996) as well as in the Vα domain (Fields et al., 1995). These deviations define fundamental differences between the TCR as a cell surface receptor and antibody as a soluble immune molecule.

THE Cβ FG LOOP

First noted upon structural analysis was the striking elongation of the FG loop of the Cβ domain connecting its F and G β-strands. Compared to other Ig-like structures, there is a 13 amino acid (aa)

Mechanotransduction is a basis for receptor signaling in many biological systems. Recent data based upon optical tweezer experiments suggest that the TCR is an anisotropic mechanosensor, converting mechanical energy into biochemical signals upon specific peptide-MHC complex (pMHC) ligation. Tangential force applied along the pseudo-two-fold symmetry axis of the TCR complex post-ligation results in the αβ heterodimer exerting torque on the CD3 heterodimers as a consequence of molecular movement at the T cell–APC interface. Accompanying TCR quaternary change likely fosters signaling via the lipid bilayer predicated on the magnitude and direction of the TCR–pMHC force. TCR glycans may modulate quaternary change, thereby altering signaling outcome as might the redox state of the CxxC motifs located proximal to the TM segments in the heterodimeric CD3 subunits. Predicted alterations in TCR TM segments and surrounding lipid will convert ectodomain ligation into the earliest intracellular signaling events.

Keywords: quaternary change, mechanosensor, T cell signaling, force transduction, antigen recognition
ABED cannot be replaced by the isologous CD3 ectodomains and foster quaternary change (see Glossary) that with CD3 cell surface membrane. As indicated below, this asymmetric cavity region (Kim et al., 2010).

The uniquely kinked conformation of the CD3γ subunit's extracellular domains and CD3εγ revealed a unique side-to-side hydrophobic interface with conjoined β-sheets between the two C/C2-set Ig-like ectodomains. The parallel pairing of these rigidified dimer modules is a striking structural feature not observed elsewhere (Sun et al., 2001, 2004; Arnett et al., 2004; Kjer-Nielsen et al., 2004). Whereas the CD3ε subunit conformation is virtually identical in CD3εγ and CD3δε, the CD3δ ectodomain adopts a C-set Ig fold with a narrower GFC front face β-sheet that is more parallel to the ABED back face than those β-sheets in CD3ε and CD3γ. The dimer interface between CD3δ and CD3ε is highly conserved among species and of similar character as in CD3εγ. Glycosylation sites in CD3δ are arranged such that the glycans may point away from the membrane, consistent with a model of TCR assembly that allows the CD3δ chain to be in close contact with the TCR α chain (Figure 1B). The rigidified CD3 heterodimers are associated with the TCR αβ heterodimer whose own rigid structure is reinforced by the FG loop and peculiar αβ asymmetry in constant domains. Thus, not unexpectedly, comparison of unligated and pMHC ligated TCR αβ structures does not show major conformational changes (reviewed in Rudolph et al., 2006).

A model of the TCR complex of αβ, CD3εγ, and CD3δε ectodomains (Sun et al., 2004) defines a plausible topology and emphasizes its glycan richness (Figure 1B). Given that CD3ε has only a nine amino acid long ectosegment, its extracellular segment is omitted from the Figure as are the connecting peptides (CP) of the TCR α and β chains and the stalk regions of CD3ε, CD3γ, and CD3δ. This rendering incorporates the consequences of several known TCR characteristics: (i) putative transmembrane charge pairs involving TCR subunit chain association with CD3ε−CD3δ−TCRα−CD3γ−CD3δε as one cluster and CD3ε−CD3γ−TCRβ as a second cluster (Call et al., 2002, 2004), (ii) extracellular domain associations involving other in vitro chain association data (Manolios et al., 1991, 1994), TCR crosslinking results (Brenner, 1985; Koning et al., 1990), and (iii) proximity of one CD3ε subunit to the TCR αβ FG loop revealed by quantitative T cell surface immunofluorescent antibody binding analysis (Ghendler et al., 1998). In addition, structural insights from crystallographic data on the glycosylated N15 TCRαβ heterodimer ectodomain in complex with H57 Fab and the likely position of glycans in both CD3εγ and CD3δε (Wang et al., 1998) are considered. Specifically, CD3εγ is presumed to be near the cavity formed between the TCR Ca, CD, EF loops, and the αβ FG loop (Ghendler et al., 1998; Wang et al., 1998). Residues in the TCR Ca AB loop which shows significant conformational change for a LC13 TCR upon pMHC binding (Kjer-Nielsen et al., 2003) were used as target sites for CD3εγ docking in the initial search for possible docking models. CD3δε is docked on the opposite site of the TCR αβ domain where there are less glycans to interfere with the more heavily glycosylated CD3δ subunit (Figure 1B), and consistent with known TCRα and CD3δ TM associations from biochemical analysis (Call et al., 2002).

The multiple N-linked glycan adducts of the TCR complex (Figure 1B, top panel) help guide pMHC ligands to the TCR recognition surface, reducing entropic penalties by directing binding to the exposed, glycan-free CDR loops. Glycans may also serve a regulatory function, contributing to a galectin–glycoprotein lattice (Demetriou et al., 2001). The more heavily glycosylated CD3δ subunit may influence TCR subunit assembly through steric constraints. The distribution of glycans in the model shown in Figure 1B is also consistent with the lack of mAbs elicited against the native CD3δ and CD3γ subunits. Importantly, glycans are large and dynamic. These adducts can affect movement of TCR

A DENSE N-LINKED GLYCAN ARRAY DECORATES THE TCR

The NMR and X-ray structures of CD3εγ and CD3δε revealed a unique side-to-side hydrophobic interface with conjoined β-sheets between the two C/C2-set Ig-like ectodomains. The parallel pairing of these rigidified dimer modules is a striking structural feature not observed elsewhere (Sun et al., 2001, 2004; Arnett et al., 2004; Kjer-Nielsen et al., 2004). Whereas the CD3ε subunit conformation is virtually identical in CD3εγ and CD3δε, the CD3δ ectodomain adopts a C-set Ig fold with a narrower GFC front face β-sheet that is more parallel to the ABED back face than those β-sheets in CD3ε and CD3γ. The dimer interface between CD3δ and CD3ε is highly conserved among species and of similar character as in CD3εγ. Glycosylation sites in CD3δ are arranged such that the glycans may point away from the membrane, consistent with a model of TCR assembly that allows the CD3δ chain to be in close contact with the TCR α chain (Figure 1B). The rigidified CD3 heterodimers are associated with the TCR αβ heterodimer whose own rigid structure is reinforced by the FG loop and peculiar αβ asymmetry in constant domains. Thus, not unexpectedly, comparison of unligated and pMHC ligated TCR αβ structures does not show major conformational changes (reviewed in Rudolph et al., 2006).

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FIGURE 1 | Continued.
subunits, thereby impacting signaling. Consistent with this notion, TCR functional avidity was altered by removal of the Ca glycan (Kuball et al., 2009).

Immediately evident in Figure 1B (bottom panel) is the central position of the TCR αβ heterodimer with a vertical dimension of 80 Å projecting from the cell membrane, flanked on either side by the shorter (40 Å) CD3 heterodimers, CD3εδx and CD3εγ with the “left” TCRα side and CD3εγ on the “right” TCRβ side. Note that the width of the CD3εδ and CD3εγ components, 50 and 55 Å, respectively, are comparable in size to that of the TCRαβ heterodimer (58 Å), and together (excluding glycans) span ~160 Å. These flanking CD3 ectodomain components will likely impede lateral movement of the TCRβ heterodimer upon pMHC binding. As previously noted for CD3εγ (Sun et al., 2001), the intradomain disulfide bridge between Cys residues on the B and F strands at the center of each CD3εδ domain reinforces the domain structure. Further rigidity for potential signal transduction comes from the paired G-β-strands in each CD3 heterodimer, coupled with the conserved RxCxxCxΕ cysteine-coordinated stalks (Sasada et al., 2002) discussed in a separate section.

DYNAMIC QUATERNARY CHANGE UPON TCR LIGATION

The length of the CD3 subunit stalks (5–10 amino acids) is typical for transmembrane proteins observed, for example, for CD2, CD4, and CD58. On the other hand, the CP found in TCRα (25–26 aa) and TCRβ (19 aa) are long. The latter are probably mandated by a requirement for a linker segment of sufficient length to span the 50 Å from the end of the interchain disulfide of the TCR α constant domain to the associated CD3ε and CD3δ transmembrane (TM) segments which are juxtaposed for apparent charge pairing (i.e., between the TCRα Φyline and aspartic residues of CD3ε and CD3δ TM, respectively). Similar considerations must be applied to the TCRβ connecting peptide, with charged pairing of the TM TCRβ Φyline with an aspartic and a glutamic acid residue of CD3ε and CD3γ TM, respectively. Note that the TCRα TM also includes an arginine residue that is thought to form a charged pair with an aspartic residue in each of the CD3ζ TM segments (Call et al., 2002).

We hypothesize that, based on the structures of CD3εδ and CD3εγ, the highly selective TCR signaling may require dynamic interaction rather than static on-and-off switching, such that the interfaces between the extracellular domains of the TCR αβ heterodimer and CD3 dimers may be quite small. With this current model, no detailed information on the interfaces is warranted, being one of a range of acceptable structures. Nonetheless, we envisage the ectodomains of TCR αβ chains being supported by the CD3 heterodimers, while components of the TCR αβ dimer, such as the Cβ FG loop (Wang et al., 1998) and the α-CP (Backström et al., 1998; Werlen et al., 2000) may serve as levers and/or tension elements to help control vertical movements of CD3 subunits for signal transduction through the critical TM segments. Given apparently weak ectodomain association between CD3 and TCR αβ heterodimers (see Arnett et al., 2004; Touma et al., 2007 and references therein), it is likely that this assembly undergoes dynamic quaternary change upon TCR ligation and triggering, thereby affecting cytoplasmic CD3 signaling regions. According to the model, the five helices of the CD3ε–CD3δ–TCRα–CD3ζ–CD3ϵ component lie closer to the TCR α subunit and the three helices of the CD3ε–CD3γ–TCRβ component lie closer to the TCRβ subunit (Call et al., 2002).

THE TCR AS AN ANISOTROPIC MECHANOSENSOR

The squat and rigid CD3 connecting segments (Touma et al., 2007) contrast sharply with the long and flexible TCR α and β CP linking their respective constant domains to the transmembrane segments. Structural insight into a basis for this contrasting arrangement first came from analysis of interactions of activating and non-activating anti-CD3ε monoclonal antibodies, which bind to the CD3εγ ectodomains with virtually identical affinity on T cells. Activating antibodies footprint to the membrane distal CD3ε lobe which they approach diagonally, adjacent to the lever-like Cβ FG loop noted above to facilitate pMHC-triggered activation. In contrast, a non-activating mAb (17A2) was found to bind to the clef between CD3ε and γ in a perpendicular mode (Kim et al., 2009; Figure 1D). Thus, polystyrene bead-bound 17A2 antibody became stimulatory only upon application of ~50 pN of external tangential force to the bead. Specific bead-bound pMHC (but not irrelevant peptide bound to the same MHC) activates a T cell upon application of a similar force via optical tweezers to initiate intracellular calcium flux (Figure 2). These findings imply that the TCR is a mechanosensor, converting mechanical energy into a biochemical signal upon specific pMHC ligation that occurs as a T cell moves over APCs during the course of immune surveillance. As shown in Figure 1C (left panel), the pMHC on the APC is first ligated by a specific TCR. However, as the T cell continues to move prior to a stop movement signal mediated through inside-out integrin affinity up-regulation, pMHC functions as a force transducing handle to pull on the TCR αβ heterodimer (Figure 1C,
right panel). This force is amplified and exerted on CD3εγ by the lever arm where the TCRβ TM acts as a fulcrum. For activation, force must be applied to the TCR complex tangentially and not perpendicular to the plane of the T cell membrane, showing that the TCR is an anisotropic mechanosensor (i.e., direction matters; Kim et al., 2009). The rupture force and bond lifetime under load between pMHC and TCRβ heterodimer are potentially important parameters which can determine the potency of pMHC stimulation. The pull from pMHC most probably causes the Cβ FG loop to push on the upper outer lobe of CD3ε. During this force driven quaternary change, TCR-decorating glycans can serve as steric and spring-like barriers that require force to overcome in order to deliver signaling to CD3 subunits. Several groups have recently provided evidence that physical force applied to TCR components activates T cells (Kim et al., 2009; Li et al., 2010; Ma and Finkel, 2010; Husson et al., 2011; Judokusumo et al., 2012).

That the TCR is a mechanosensor activated by direction-specific physical force has several immediate implications. First, since the total force applied to the T cell surface is essentially perpendicular to the plane of the T cell membrane, showing that the TCR is an anisotropic mechanosensor (i.e., direction matters; Kim et al., 2009). The rupture force and bond lifetime under load between pMHC and TCRβ heterodimer are potentially important parameters which can determine the potency of pMHC stimulation. The pull from pMHC most probably causes the Cβ FG loop to push on the upper outer lobe of CD3ε. During this force driven quaternary change, TCR-decorating glycans can serve as steric and spring-like barriers that require force to overcome in order to deliver signaling to CD3 subunits. Several groups have recently provided evidence that physical force applied to TCR components activates T cells (Kim et al., 2009; Li et al., 2010; Ma and Finkel, 2010; Husson et al., 2011; Judokusumo et al., 2012).

The lifetime of TCR–pMHC bonding where it is maximal at certain force levels enabling specific pMHC ligand to drive quaternary change, yet allow for quick release for other pMHC ligand binding. Because the torque exerted by the TCR–pMHC interaction around the Cβ FG loop/CD3εγ “flywheel” is dependent on the force applied, the length of the Cβ–pMHC lever arm and the angle between the force vector and lever arm, TCR docking topology is important.

Consistent with this view, a recent paper demonstrated that docking orientation rather than affinity of 3D binding correlated with the ligand’s T cell activating potential (Adams et al., 2011). This finding is also in agreement with a docking orientation difference between the T cell activating 2C11 versus non-activating 17A2 antibodies (Kim et al., 2009; Figure 1D). Bacterial superantigens stimulate up to 20% of the entire T cell population by simultaneously interacting with class II MHC and TCRβ molecules on APC and T cells, respectively (Sundberg et al., 2002). Not surprisingly, therefore, these interactions foster TCR docking vectors similar to those of activating TCR–pMHC interactions (Reinherz et al., 1999). Precedent for mechanoreceptors in the hematopoietic system is the von Willebrand factor (VWF) receptor on platelets where tensile stress on bonds between the GPⅠbα subunit and the VWFA1 domain under fluid dynamic conditions triggers integrin αⅠbβⅢ activation to support platelet adhesion (Doggart et al., 2002; Ruggeri, 2007).

**THE CxxC MOTIF IN CD3ε, CD3γ, AND CD3ζ: A POTENTIAL ROLE IN STRUCTURAL STABILIZATION AND REDOX SENSITIVE SIGNALING ATTENUATION**

Studies on murine CD3γ (Touma et al., 2007) and human CD3γ (Thomassen et al., 2006; Xu et al., 2006) attest to the importance of the cysteines in the CxxC motif for TCR function and/or assembly. Similar findings have been shown for CD3ζ (Martinez-Martín et al., 2009; Wang et al., 2009). Given that the two cysteines in each CD3 CxxC motif are adjacent to the TM helix (Figure 3) and in view of a recent study showing that a CxxC motif is found at the N-termini of α-helices, stabilizing α-helical structures, this juxtaposition is noteworthy (Iqbal et al., 2006). Assuming an intrachain disulfide is formed in each stalk region (vide infra), one possibility is that the CD3 TM helix is stabilized and perhaps even extended as an elongated helix above the plane of the cell membrane. Alternatively, this CxxC motif may support a tight β turn (Hsu et al., 2006). In either case, the disposition of the CD3 ectodomain relative to the cell membrane may be affected if a disulfide bond is removed, attenuating signaling, and altering TCR quaternary structure. The disulfide bonds would ensure that lever action on the TM helices of the various CD3 domains would be simultaneous, parallel, and in phase. Whether physiologic modification of the redox state of the CD3 heterodimer is regulated during development or T cell activation can be determined. However, given that TCR crosslinking on murine and human T lymphocytes generates hydrogen peroxide and superoxide ions (Paní et al., 2000; Devadas et al., 2002) and that oxidative stress from macrophages alters the native CD3ζ association with the TCR (Otsuji et al., 1996), it is possible that redox reactivity of CD3 stalk cysteines is critical for modulating TCR quaternary structure, subunit conformation, and functional responsiveness. Rapid conversion between oxidized and reduced forms under...
physiologic circumstances may be important for TCR triggering and downregulation, respectively. Assuming a direct link between redox state, TCR function, and TM structure is demonstrated, future efforts can be directed toward design of deliverable redox regulators using mAb or other materials to modify T cell responses.

MECANOSENSING AT THE IMMUNOLOGICAL SYNAPSE

Our data involve a model wherein tangential forces applied along the pseudo-two-fold symmetry axis of the TCR αβ heterodimer exerts a highly selective signaling torque on the CD3 components. This directionally specified vector precludes non-specific activation and fosters antigen-specific events. In turn, activation leads to stop movement and formation of the immunological synapse. Mechanoreceptor function is most likely additionally tunable by inducible actin cytoskeletal interactions with TCR and pMHC on T cells and APCs, respectively, since torque will be greatest in their presence. Within the synapse, force could be generated on the TCR via microcluster formation and actin-based trafficking (Yokosuka et al., 2008). Mecanosensing can be further amplified at the synapse where intermembrane distances (~150 Å) are optimal for TCR/pMHC ligation in conjunction with other signaling molecules to sustain activation from both p-SMAC and c-SMAC components. The facilitating roles of adhesion molecules to sustain activation from both p-SMAC and c-SMAC components. The facilitating roles of adhesion molecules to sustain activation from both p-SMAC and c-SMAC components. The facilitating roles of adhesion molecules to sustain activation from both p-SMAC and c-SMAC components.
Tensile force  
Force which acts perpendicular to a surface, like the force on a rope.

Catch bond  
Type of intermolecular bonds which strengthens upon application of force. Typically, force accelerates bond breakage as in “slip bonds.”

Torque  
The tendency of force to generate rotation of a body about an axis.

Lever  
Force amplifying device which consists of a fulcrum, fixed pivot, and a rigid beam.

Chemical force  
Force derived from intermolecular bonding.

Mechanotransduction  
Cell signaling through means of a mechanical input.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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