Published in final edited form as:

J Mol Med (Berl). 2014 July ; 92(7): 735–741. doi:10.1007/s00109-014-1145-2.

Molecules in medicine mini review: the $\alpha\beta$ T cell receptor

Eric T. Clambey,

Department of Anesthesiology, Mucosal Inflammation Program, University of Colorado School of Medicine, Mail Stop B112, Research Complex 2, 12700 East 19th Avenue, Aurora, CO 80045, USA. Integrated Department of Immunology, University of Colorado Denver and National Jewish Health, Denver, CO, USA

Bennett Davenport,

Department of Anesthesiology, Mucosal Inflammation Program, University of Colorado School of Medicine, Mail Stop B112, Research Complex 2, 12700 East 19th Avenue, Aurora, CO 80045, USA. Integrated Department of Immunology, University of Colorado Denver and National Jewish Health, Denver, CO, USA

John W. Kappler,

Integrated Department of Immunology, University of Colorado Denver and National Jewish Health, Denver, CO, USA. Howard Hughes Medical Institute, National Jewish Health, Denver, CO, USA

Philippa Marrack, and

Integrated Department of Immunology, University of Colorado Denver and National Jewish Health, Denver, CO, USA. Howard Hughes Medical Institute, National Jewish Health, Denver, CO, USA

Dirk Homann

Department of Anesthesiology, Mucosal Inflammation Program, University of Colorado School of Medicine, Mail Stop B112, Research Complex 2, 12700 East 19th Avenue, Aurora, CO 80045, USA. Integrated Department of Immunology, University of Colorado Denver and National Jewish Health, Denver, CO, USA

Eric T. Clambey: eric.clambey@ucdenver.edu; Dirk Homann: dirk.homann@ucdenver.edu

Abstract

As an integral part of the mammalian immune system, a distributed network of tissues, cells, and extra-cellular factors, T lymphocytes perform and control a multitude of activities that collectively contribute to the effective establishment, maintenance, and restoration of tissue and organismal integrity. Development and function of T cells is controlled by the T cell receptor (TCR), a heterodimeric cell surface protein uniquely expressed on T cells. During T cell development, the TCR undergoes extensive somatic diversification that generates a diverse T cell repertoire capable of recognizing an extraordinary range of protein and nonprotein antigens presented in the context of major histocompatibility complex molecules (MHC). In this review, we provide an introduction to the TCR, describing underlying principles that position this molecule as a central regulator of

the adaptive immune system involved in responses ranging from tissue protection and preservation to pathology and autoimmunity.

Keywords

Tcell receptor; Major histocompatibility complex; Tcell repertoire

T cells and their receptors

T cells, named in reference to the thymus as the principal site for their “primary education,” are a major class of lymphocytes that are essential for the generation, maintenance, adaptation, and restoration of immune homeostasis under physiological and pathophysiological conditions, and thus provide a critical contribution to the preservation of tissue and organismal integrity. Their distinctive property is a heterodimeric cell surface receptor composed in the majority of vertebrate T cells of so-called alpha and beta chains that together form the $\alpha\beta$ T cell antigen receptor (here abbreviated as TCR, see Fig. 1). The antigens recognized by the TCR are peptide fragments of endogenous or exogenous origin bound to and presented by major histocompatibility complex (MHC) proteins that cover the surface of most cells in the body. The coevolution of TCR and MHC proteins has produced a formidable recognition system that can translate minor structural changes among MHC-bound peptides into sweeping, adaptable, and coordinated T cell responses that include cellular activation, proliferative expansion and differentiation, dissemination across most organs, acquisition and deployment of effector functions, as well as eventual T cell death or extended survival. The resultant balance of tissue pathology, preservation, and/or protection is therefore a direct function of the TCR-dependent initiation and regulation of T cell immunity.

The discovery of the TCR some 30 years ago constituted the culmination of concerted efforts that pushed the limits of available technology to identify and characterize the TCR protein as a pair of clone-specific, disulfide-linked heterodimeric polypeptide chains composed of both constant and variable regions [1–4], and to decipher the basic organization of the genes encoding these chains [5–8]. Collectively, these reports provided the technological and conceptual basis for a transition from cellular phenomenology to targeted molecular, structural, and functional T cell studies [9] and paved the way for the subsequent three decades worth of ever-accelerating research that have expanded and enriched our understanding of T cell biology at large. Here, we provide a brief overview over one of the most intricate receptor structures known in the mammalian immune system and sketch out some of the clinically relevant aspects of TCR biology in health and disease.

Generation of diversity—TCR formation by somatic recombination

Unlike conventional proteins that are encoded by a single germline-encoded gene, TCR genes are assembled from a large set of noncontiguous gene segments in a stochastic process known as V(D)J recombination. TCR diversity is further increased by the nontemplate addition or deletion of nucleotides at the junctions between gene segments, and by the pairing of two polypeptide chains that are required to form a mature TCR. The

combinatorial diversity generated by V(D)J recombination of the two TCR chains is truly astounding and has been estimated to exceed 10^{15} potential TCRs [10]. Diversity, it should be noted, is not allocated evenly across the TCR but focused on the variable regions of the TCR gene segments, especially in the highly variable complementarity determining regions (CDR) 1, 2, and 3. The CDRs are the principal sites of contact with which TCRs bind to their similarly diverse ligands that are composed of individual peptide fragments presented in the context of MHC molecules (pMHC complexes). Other parts of the TCR contain conserved structural elements that serve as a scaffold for the variable TCR portions, anchor the TCR in the T cell membrane, and associate with a complex of signal transduction molecules (see below).

Pruning of diversity—TCR selection in the thymus

While V(D)J recombination can generate extraordinary TCR diversity, not all TCRs can be accommodated and utilized by the immune system. A successfully rearranged TCR in the thymus must meet two criteria that are contingent on the physical properties that define the interactions between TCRs and their ligands: (1) any TCR should be able to bind to and recognize pMHC complexes in the thymus (positive selection), while (2) not having too high of an affinity for pMHC complexes expressed within the thymus (negative selection). Positive and negative selections may therefore reduce TCR repertoire diversity by up to 100-fold [10] making the thymus a virtual graveyard for nascent T cells. Importantly, this process of “central tolerance” ensures that most of the mature T cells exported into the periphery will productively react with pMHC complexes containing peptides derived from “foreign” sources (e.g., pathogens) yet exhibit a significantly reduced ability to respond to pMHC complexes incorporating peptides derived from proteins of their own host, removing potentially autoreactive TCR specificities. Redirection of autoreactive TCRs can be further accomplished by developmentally diverting autoreactive T cells to the regulatory T cell lineage, a potent inhibitory subset of T cells (see below), or by the induction of secondary TCR rearrangements either in the thymus or in the periphery [11]. A balanced peripheral T cell repertoire is critical for the TCR-dependent recognition of a diverse array of pathogens [10], and any processes that enhance or reduce T cell diversity may promote immune pathologies or compromise immune protection. For example, the more limited TCR diversity observed in the elderly as a consequence of thymic involution and oligoclonal T cell expansions is thought to contribute to impaired immune responses in aged individuals [12] while the insufficient removal of TCRs that react against peptides derived from endogenous cellular proteins (“self-peptides”) is thought to be a primary driver of T cell-mediated autoimmunity (e.g., type 1 diabetes) [13, 14].

T cell specificity and T cell fate

The rearrangement of a productive, protein-coding TCR has the potential to confer more than specificity to a T cell. Indeed, different TCRs are associated with conveying subspecialized fates among T cells. For example, a TCR that primarily recognizes a peptide in the context of an MHC class I molecule (MHC-I) will develop into a CD8⁺ T cell in the thymus, whereas a TCR that primarily recognizes a peptide in the context of an MHC class II molecule (MHC-II) will develop into a CD4⁺ T cell (CD8 and CD4 are coreceptors that

bind to MHC-I and MHC-II, respectively). Furthermore, expression of certain TCRs can convey additional, specialized functions to T cells in the periphery. These include natural killer T (NKT) and mucosal associated invariant T (MAIT) cells, that are characterized by a highly focused, semi-invariant usage of certain TCR rearrangements [15, 16] as well as regulatory T cells which, in many cases, are characterized by TCRs that have a higher affinity for self-encoded peptides [17].

TCR recognition—the trimolecular complex and beyond

By itself, the TCR is incomplete. TCR recognition requires a trimolecular convergence of the TCR (expressed on the T cell) and a stimulating ligand (typically an 8–20 amino acid peptide) presented in the context of MHC-I or MHC-II, a phenomenon referred to as MHC restriction (Fig. 1). This process ensures that the TCR encounters its stimulating ligand in the context of another cell (e.g., an antigen presenting cell in the case of T cell activation or somatic cells in the case of T cell-mediated tissue destruction) and distinguishes the TCR from antibodies that can bind to antigen in the absence of MHC. Peptides presented by MHC molecules are derived from proteasomal or endosomal degradation of cellular or exogenous (e.g., pathogen-derived) proteins. Notably, MHC molecules are a highly polymorphic group of genes that exhibit wide interindividual variation. Polymorphisms within the MHC gene family are particularly prominent in the peptide-binding pocket. The high rate of interindividual variation in MHC genes and the extraordinary diversity of TCRs present in each individual, presents a prominent challenge in understanding the molecular basis of TCR recognition.

TCRs most often recognize native, unmodified peptides presented in the context of MHC. Alternatively, TCRs can recognize peptides that have either been posttranslationally modified [14, 18, 19] or whose structure and binding to MHC is perturbed by the presence of nonpeptide molecules such as metal ions [20]. TCR reactivity to modified peptides is thought to underlie certain types of immune pathologies including rheumatoid arthritis, where RA patients have an anti-citrullinated peptide response [21], and chronic beryllium disease, where patients have an inappropriate reactivity to the metal ion beryllium [22].

Some TCRs can recognize nonpeptide ligands presented in the context of nonclassical MHC family members. The best known of these are invariant TCRs expressed primarily by the natural killer T (NKT) cell subset that recognize lipids presented in the context of the CD1 protein, an MHC-like molecule [23, 24]. More recently, TCRs expressed by the MAIT subset of T cells have been found to recognize microbially derived riboflavin metabolites presented in the context of the MR1 protein, another MHC-like molecule [25, 26]. How exactly the TCR discriminates between different ligands presented in the context of polymorphic MHC molecules remains a central question for modern immunology studies that is central to understanding host defense and autoimmunity.

Preferential TCR reactivity with MHC

Productive TCR:pMHC interactions are of a “hybrid nature” that poses some intriguing conceptual challenges. For one, the TCRs of mature T cells need to react with elements of both “self” (MHC) and “non-self” (e.g., pathogen-derived peptides) subverting the idea of a

simple “self/non-self distinction” as an organizing principle for the immune system [27]. Indeed, TCR recognition of pMHC complexes is necessary for the survival of naïve $\alpha\beta$ T cells, indicating that TCR:MHC interactions are constantly occurring at a basal level [28]. The differential allocation of reactivities in fact correlates with defined structural receptor/ligand components: a great variety of germline-encoded TCR elements (CDR1 and CDR2) preferentially binds to defined MHC domains while highly variable, nongerm-line-encoded TCR portions (CDR3) favor contacts with the MHC-bound peptide. This raises an obvious and important question: how has the coevolution of a diverse TCR repertoire together with highly polymorphic MHC loci accommodated the generation of particular constraints and freedoms that govern this extraordinarily varied collection of flexible protein:protein interactions? Ontogenetically, positive selection can account for the selection of mature T cell populations biased towards MHC reactivity from an inherently random TCR repertoire. Phylogenetically, however, the trait of positive selection likely emerged in conjunction with the evolutionary selection for TCR elements that are prone, within the limits of effective self-tolerance, to engage MHC rather than other ligands. If so, the result should be a germline bias that skews the “unselected” T cell repertoire towards potentially useful, i.e., MHC-reactive TCR determinants. Evidence for this “evolutionary hypothesis” has recently been obtained for particular murine TCR families [29]. While the degrees of freedom bestowed by TCR diversity and MHC polymorphisms would make any generalization at present somewhat premature, eventual delineation of the rules informing preferential TCR:MHC engagement will likely have important implications, in particular for our understanding of tumor immunity, alloimmunity (e.g., during transplant), and autoimmunity.

TCR specificity, affinity, signal transduction, and the T cell response

The TCR has a remarkable ability to discriminate between different peptides (e.g., discriminating between two peptides that differ only by a single amino acid) [30, 31], yet the affinity between a specific TCR and its pMHC complex is relatively low (in the 10^{-6} M range of affinities) [32, 33]. This is in contrast to antibodies, which bind to antigens with a much higher affinity (e.g., in the 10^{-9} M range of affinities).

The TCR heterodimer itself is incapable of transducing signals into the T cell. Instead, the TCR heterodimer is in close physical association with a complex of signal transduction molecules including the CD3 family of proteins (CD3 δ , CD3 ϵ , CD3 γ) and the zeta chain (Fig. 1). Upon TCR binding to its specific ligand, a cascade of signal transduction events is activated by these associated molecules. The precise mechanism by which TCR binding to a peptide/MHC complex triggers signal transduction remains an area of intense study with multiple potential models actively under consideration [34–36]. Notably, in order for a T cell to be fully activated, TCR signaling must occur in close temporal and spatial proximity with additional signal transduction cascades; these include activation through costimulatory molecules (e.g., signaling through CD28 and CD28-related proteins [37]) and through locally produced cytokines such as IL-12 and type I interferons that allow maximal T cell activation [38]. Conversely, TCR signaling can be dampened by coengagement of inhibitory receptors [39]. Insufficient TCR signaling can result in various hyporesponsive states (e.g., peripheral tolerance, exhaustion, and anergy), characterized by impaired proliferation and/or effector function [40]. The integration of TCR signaling with these additional positive and

negative inputs [41] ensures that T cell activation is constrained to the appropriate time and cellular context.

Activation through the TCR coupled with the integration of multiple signaling events rapidly elicits a specific T cell response that is chiefly characterized by proliferation and the acquisition of effector functions. The proliferative expansion of specific T cells ensures that sufficiently large populations of effector T cells are generated from a very limited pool of naïve T cells present in the periphery. In parallel to proliferation and expansion, specific T cells undergo a “secondary education” that culminates in the acquisition and elaboration of effector activities such as cytokine production (e.g., by CD4⁺ “helper” T cells which can alter the properties of both T and other cells) or targeted cell killing (e.g., the capacity of “cytotoxic” CD8⁺ T cells to cause death of infected or tumor cells). As such, activation through the TCR serves as a potent selection force to rapidly expand and engage functional properties of a highly specific set of T cells.

While the individual frequency of an individual TCR that can respond to any particular infection is low (comprised only of hundreds to thousands of T cells expressing a specific TCR out of the millions of T cells in the body), there are contexts in which cross-reactive TCRs or a relatively high frequency of TCRs, and T cells, can be activated. First, though an individual TCR has the ability to discriminate between closely related peptides, a single TCR can recognize more than one peptide, a phenomenon referred to as “heterologous immunity” that is thought to contribute to both anti-viral and alloimmune responses [42]. Second, a disproportionately large number of TCRs have been found to be activated in two divergent medical contexts: (1) in response to microbial-encoded superantigens [43, 44] and (2) in response to the detection of allogeneic MHC molecules, a situation that frequently occurs in the context of organ transplantation between genetically unrelated donors [45, 46]. In both contexts, activation of a large frequency of T cells is thought to contribute to excessive immune responses and to resulting immune-mediated pathology.

Selected clinical applications

The identification, quantification, characterization, isolation, and targeted manipulation of specific T cell populations constitute the principal goal for a diverse array of diagnostic, prophylactic, and/or therapeutic interventions. Given the central role of the TCR in conveying T cell specificity and reactivity, the TCR remains at the heart of many current and future clinical applications that ultimately seek to restrain pathogenic T cell immunity (autoimmune diseases) or to embellish protective (infectious and neoplastic diseases) or regulatory (autoimmunity) T cell responses. Since a comprehensive discussion of these topics is well beyond the scope of this review, we will restrict our discussion to two examples that illustrate the power of translating insights into TCR biology to a clinical context. First, beginning in the mid-1990s, a technological revolution provided unprecedented analytical access to specific T cell populations as defined by their TCR expression. Based on major advances in protein biochemistry, recombinant pMHC complexes were generated and deployed as probes (“pMHC multimers” tagged with fluorescent dyes or, more recently, caged metal ions) that only bind to specific TCRs and thus permit the direct ex vivo visualization of corresponding T cell populations [47–49].

Similarly, short-term in vitro assays were developed (“intra-cellular cytokine staining”) to identify and functionally characterize specific T cell populations. In combination, these technologies have enabled the accurate monitoring of T cell responses in a great variety of experimental and clinical settings (e.g., specific T cell populations generated in the wake of established and novel vaccination regimens [50, 51]). Second, over the past decade, investigators have demonstrated the potential of redirecting T cells and their reactivity beyond the T cell receptor. The best described of these is the development of chimeric antigen receptors (CARs), which when introduced into T cells convey a new specificity and reactivity within T cells [52]. Though this method is not currently amenable to large-scale adoption in the clinic, CAR-modified T cells have already been used in clinical trials where they have been shown to have efficacy in promoting anti-tumor control [52, 53]. One notable property of many of the CAR-modified T cell therapies is that the chimeric antigen receptor used is comprised of an antibody-derived fragment directly fused to TCR signaling machinery; this artificial “chimera” endows specificity to the T cell beyond conventional restriction by MHC molecules. This MHC-independent method of T cell reactivity is notable since it allows this method to be used despite the high degree of interindividual variation in MHC haplotypes found in humans.

Conclusion

The $\alpha\beta$ TCR constitutes a prime example for the principal functions of the vertebrate immune system: the balance of recognition and reactivity, pathology and protection, immune defense, and homeostasis (and, for that matter, for the “Goldilocks principle” of immunobiology). Ranging from the phenomenon of somatic recombination to the adoptive transfer of engineered T cells, the TCR occupies a pivotal position at the intersection between health and disease. We have no doubt that the continued work on TCR biology will reveal additional principles fundamental to host defense and survival and to carve out new avenues for clinical interventions.

Acknowledgments

This work was supported by NIH grants AG026518 and AI093637, JDRF CDA 2-2007-240 (DH) and American Heart Association grant 13SDG14510023 (ETC.).

References

1. Allison JP, McIntyre BW, Bloch D. Tumor-specific antigen of murine T-lymphoma defined with monoclonal antibody. *J Immunol.* 1982; 129:2293–2300. [PubMed: 6181166]
2. Meuer SC, Fitzgerald KA, Hussey RE, Hodgdon JC, Schlossman SF, Reinherz EL. Clonotypic structures involved in antigen-specific human T cell function. Relationship to the T3 molecular complex. *J Exp Med.* 1983; 157:705–719. [PubMed: 6185617]
3. Haskins K, Kubo R, White J, Pigeon M, Kappler J, Marrack P. The major histocompatibility complex-restricted antigen receptor on T cells. I. Isolation with a monoclonal antibody. *J Exp Med.* 1983; 157:1149–1169. [PubMed: 6601175]
4. Kappler J, Kubo R, Haskins K, Hannum C, Marrack P, Pigeon M, McIntyre B, Allison J, Trowbridge I. The major histocompatibility complex-restricted antigen receptor on T cells in mouse and man: identification of constant and variable peptides. *Cell.* 1983; 35:295–302. [PubMed: 6605199]

5. Hedrick SM, Cohen DI, Nielsen EA, Davis MM. Isolation of cDNA clones encoding T cell-specific membrane-associated proteins. *Nature*. 1984; 308:149–153. [PubMed: 6199676]
6. Hedrick SM, Nielsen EA, Kavaler J, Cohen DI, Davis MM. Sequence relationships between putative T-cell receptor polypeptides and immunoglobulins. *Nature*. 1984; 308:153–158. [PubMed: 6546606]
7. Chien YH, Gascoigne NR, Kavaler J, Lee NE, Davis MM. Somatic recombination in a murine T-cell receptor gene. *Nature*. 1984; 309:322–326. [PubMed: 6328306]
8. Yanagi Y, Yoshikai Y, Leggett K, Clark SP, Aleksander I, Mak TW. A human T cell-specific cDNA clone encodes a protein having extensive homology to immunoglobulin chains. *Nature*. 1984; 308:145–149. [PubMed: 6336315]
9. Weiss A. Discovering the TCR beta-chain by subtraction. *J Immunol*. 2005; 175:2769–2770. [PubMed: 16116159]
10. Nikolich-Zugich J, Slifka MK, Messaoudi I. The many important facets of T-cell repertoire diversity. *Nat Rev Immunol*. 2004; 4:123–132. [PubMed: 15040585]
11. Hale JS, Fink PJ. T-cell receptor revision: friend or foe? *Immunology*. 2010; 129:467–473. [PubMed: 20201984]
12. Yager EJ, Ahmed M, Lanzer K, Randall TD, Woodland DL, Blackman MA. Age-associated decline in T cell repertoire diversity leads to holes in the repertoire and impaired immunity to influenza virus. *J Exp Med*. 2008; 205:711–723. [PubMed: 18332179]
13. Cheng MH, Anderson MS. Monogenic autoimmunity. *Annu Rev Immunol*. 2012; 30:393–427. [PubMed: 22224765]
14. Marrack P, Kappler JW. Do MHCII-presented neoantigens drive type 1 diabetes and other autoimmune diseases? *Cold Spring Harbor perspectives in medicine*. 2012; 2:a007765. [PubMed: 22951444]
15. Sullivan BA, Kronenberg M. TCR-mediated recognition of glycolipid CD1 complexes. *Curr Top Microbiol Immunol*. 2007; 314:165–193. [PubMed: 17593661]
16. Le Bourhis L, Guerri L, Dusseaux M, Martin E, Soudais C, Lantz O. Mucosal-associated invariant T cells: unconventional development and function. *Trends Immunol*. 2011; 32:212–218. [PubMed: 21459674]
17. Lee HM, Bautista JL, Scott-Browne J, Mohan JF, Hsieh CS. A broad range of self-reactivity drives thymic regulatory T cell selection to limit responses to self. *Immunity*. 2012; 37:475–486. [PubMed: 22921379]
18. Herzog J, Maekawa Y, Cirrito TP, Illian BS, Unanue ER. Activated antigen-presenting cells select and present chemically modified peptides recognized by unique CD4 T cells. *Proc Natl Acad Sci U S A*. 2005; 102:7928–7933. [PubMed: 15901898]
19. Delong T, Baker RL, He J, Barbour G, Bradley B, Haskins K. Diabetogenic T-cell clones recognize an altered peptide of chromogranin A. *Diabetes*. 2012; 61:3239–3246. [PubMed: 22912420]
20. Falta MT, Pinilla C, Mack DG, Tinea AN, Crawford F, Giulianotti M, Santos R, Clayton GM, Wang Y, Zhang X, et al. Identification of beryllium-dependent peptides recognized by CD4⁺ T cells in chronic beryllium disease. *J Exp Med*. 2013; 210:1403–1418. [PubMed: 23797096]
21. Scally SW, Petersen J, Law SC, Dudek NL, Nel HJ, Loh KL, Wijeyewickrema LC, Eckle SB, van Heemst J, Pike RN, et al. A molecular basis for the association of the HLA-DRB1 locus, citrullination, and rheumatoid arthritis. *J Exp Med*. 2013; 210:2569–2582. [PubMed: 24190431]
22. Dai S, Falta MT, Bowerman NA, McKee AS, Fontenot AP. T cell recognition of beryllium. *Curr Opin Immunol*. 2013
23. Mallevaey T, Clarke AJ, Scott-Browne JP, Young MH, Roisman LC, Pellicci DG, Patel O, Vivian JP, Matsuda JL, McCluskey J, et al. A molecular basis for NKT cell recognition of CD1d-self-antigen. *Immunity*. 2011; 34:315–326. [PubMed: 21376640]
24. Wun KS, Cameron G, Patel O, Pang SS, Pellicci DG, Sullivan LC, Keshipeddy S, Young MH, Uldrich AP, Thakur MS, et al. A molecular basis for the exquisite CD1d-restricted antigen specificity and functional responses of natural killer T cells. *Immunity*. 2011; 34:327–339. [PubMed: 21376639]

25. Kjer-Nielsen L, Patel O, Corbett AJ, Le Nours J, Meehan B, Liu L, Bhati M, Chen Z, Kostenko L, Reantragoon R, et al. MR1 presents microbial vitamin B metabolites to MAIT cells. *Nature*. 2012; 491:717–723. [PubMed: 23051753]
26. Young MH, U'Ren L, Huang S, Mallevaey T, Scott-Browne J, Crawford F, Lantz O, Hansen TH, Kappler J, Marrack P, et al. MAIT cell recognition of MR1 on bacterially infected and uninfected cells. *PLoS One*. 2013; 8:e53789. [PubMed: 23342002]
27. Coppieters, KT.; von Herrath, MG.; Homann, D. Autoimmunity and autoimmune diseases. In: Paul, W., editor. *Fundamental IMMUNOLOGY*. Lippincott Williams & Wilkins; Philadelphia: 2013.
28. Surh CD, Sprent J. Homeostasis of naive and memory T cells. *Immunity*. 2008; 29:848–862. [PubMed: 19100699]
29. Yin L, Dai S, Clayton G, Gao W, Wang Y, Kappler J, Marrack P. Recognition of self and altered self by T cells in autoimmunity and allergy. *Protein cell*. 2013; 4:8–16. [PubMed: 23307779]
30. Evavold BD, Allen PM. Separation of IL-4 production from Th cell proliferation by an altered T cell receptor ligand. *Science*. 1991; 252:1308–1310. [PubMed: 1833816]
31. Morris GP, Allen PM. How the TCR balances sensitivity and specificity for the recognition of self and pathogens. *Nat Immunol*. 2012; 13:121–128. [PubMed: 22261968]
32. Matsui K, Boniface JJ, Reay PA, Schild H, Fazekas De St Groth B, Davis MM. Low affinity interaction of peptide-MHC complexes with T cell receptors. *Science*. 1991; 254:1788–1791. [PubMed: 1763329]
33. Stone JD, Chervin AS, Kranz DM. T-cell receptor binding affinities and kinetics: impact on T-cell activity and specificity. *Immunology*. 2009; 126:165–176. [PubMed: 19125887]
34. van der Merwe PA, Dushek O. Mechanisms for T cell receptor triggering. *Nat Rev Immunol*. 2011; 11:47–55. [PubMed: 21127503]
35. Blanco R, Alarcon B. TCR nanoclusters as the framework for transmission of conformational changes and cooperativity. *Front Immunol*. 2012; 3:115. [PubMed: 22582078]
36. Kuhns MS, Davis MM. TCR Signaling Emerges from the Sum of Many Parts. *Front Immunol*. 2012; 3:159. [PubMed: 22737151]
37. Salomon B, Bluestone JA. Complexities of CD28/B7: CTLA-4 costimulatory pathways in autoimmunity and transplantation. *Annu Rev Immunol*. 2001; 19:225–252. [PubMed: 11244036]
38. Curtsinger JM, Mescher MF. Inflammatory cytokines as a third signal for T cell activation. *Curr Opin Immunol*. 2010; 22:333–340. [PubMed: 20363604]
39. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol*. 2008; 26:677–704. [PubMed: 18173375]
40. Schietinger A, Greenberg PD. Tolerance and exhaustion: defining mechanisms of T cell dysfunction. *Trends Immunol*. 2013
41. Zhu Y, Yao S, Chen L. Cell surface signaling molecules in the control of immune responses: a tide model. *Immunity*. 2011; 34:466–478. [PubMed: 21511182]
42. Selin LK, Brehm MA, Naumov YN, Cornberg M, Kim SK, Clute SC, Welsh RM. Memory of mice and men: CD8⁺ T-cell cross-reactivity and heterologous immunity. *Immunol Rev*. 2006; 211:164–181. [PubMed: 16824126]
43. Scherer MT, Ignatowicz L, Winslow GM, Kappler JW, Marrack P. Superantigens: bacterial and viral proteins that manipulate the immune system. *Annu Rev Cell Biol*. 1993; 9:101–128. [PubMed: 7506550]
44. Li H, Llera A, Malchiodi EL, Mariuzza RA. The structural basis of T cell activation by superantigens. *Annu Rev Immunol*. 1999; 17:435–466. [PubMed: 10358765]
45. Gras S, Kjer-Nielsen L, Chen Z, Rossjohn J, McCluskey J. The structural bases of direct T-cell allorecognition: implications for T-cell-mediated transplant rejection. *Immunol Cell Biol*. 2011; 89:388–395. [PubMed: 21301478]
46. Felix NJ, Allen PM. Specificity of T-cell alloreactivity. *Nat Rev Immunol*. 2007; 7:942–953. [PubMed: 18007679]
47. Altman JD, Davis MM. MHC-peptide tetramers to visualize antigen-specific T cells. *Curr Protoc Immunol*. 2003; Chapter 17(Unit 17):13.

48. Nepom GT. MHC class II tetramers. *J Immunol.* 2012; 188:2477–2482. [PubMed: 22389204]
49. Newell EW, Sigal N, Bendall SC, Nolan GP, Davis MM. Cytometry by time-of-flight shows combinatorial cytokine expression and virus-specific cell niches within a continuum of CD8⁺ T cell phenotypes. *Immunity.* 2012; 36:142–152. [PubMed: 22265676]
50. Miller JD, van der Most RG, Akondy RS, Glidewell JT, Albott S, Masopust D, Murali-Krishna K, Mahar PL, Edupuganti S, Lalor S, et al. Human effector and memory CD8⁺ T cell responses to smallpox and yellow fever vaccines. *Immunity.* 2008; 28:710–722. [PubMed: 18468462]
51. Seder RA, Chang LJ, Enama ME, Zephir KL, Sarwar UN, Gordon IJ, Holman LA, James ER, Billingsley PF, Gunasekera A, et al. Protection against malaria by intravenous immunization with a nonreplicating sporozoite vaccine. *Science.* 2013; 341:1359–1365. [PubMed: 23929949]
52. Kalos M, June CH. Adoptive T cell transfer for cancer immunotherapy in the era of synthetic biology. *Immunity.* 2013; 39:49–60. [PubMed: 23890063]
53. Rosenberg SA. Raising the bar: the curative potential of human cancer immunotherapy. *Sci Transl Med.* 2012; 4:127ps128.

IMPLICATIONS AND INDICATIONS

The T cell receptor is a heterodimeric surface protein that endows a T lymphocyte with the ability to recognize and respond against diverse antigens and infections. The T cell receptor undergoes a process of somatic diversification that creates millions of different TCR specificities, capable of responding to a huge diversity of antigens. Given its central role in conferring specificity to T cells, the TCR is a protein complex at the center of both health and disease.

- Host defense: A high diversity of TCR specificities is critical for defense against infection (e.g. an insufficient breadth of TCRs are thought to contribute to age-associated immune impairment).
- Vaccination: Targeted activation of specific TCRs through the use of vaccines has the potential to expand protective subsets of T cells that can prophylactically contain infection.
- Autoimmunity: The TCR pool undergoes a process of selection in the thymus, to ensure appropriate specificity and reactivity of T cells. Insufficient removal of TCRs that can respond to self-proteins can result in autoimmunity (e.g. type I Diabetes).
- Immunodeficiency: Defects in the generation of T cell receptors result in immunodeficiency (e.g. Severe combined immunodeficiency, SCID).

Fig. 1.

Schematic of the T cell receptor and associated molecules important for TCR recognition and signal transduction. The $\alpha\beta$ TCR is a heterodimeric cell surface receptor comprised of an alpha and beta T cell receptor chain. The TCR is in close physical association with multiple signal transducing proteins including the CD3 family of proteins and the zeta chain. The ability of a specific TCR to recognize and respond to its specific peptide requires a trimolecular interaction between the TCR and a stimulating ligand (e.g., a peptide) presented in the context of a major histocompatibility complex (MHC) molecule present on the surface of a neighboring antigen presenting cell. TCRs undergo a process of somatic diversification during their development in the thymus, resulting in a highly diverse protein coding sequence especially in areas of the TCR most exposed and likely to interact with pMHC complexes; this hypervariability is depicted by the *red lines* lining the surface of the outermost edges of the TCR