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Functional implications of T cell receptor diversity

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Summary

Naive T cells are recruited into any given host response by recognizing a spectrum of possible antigens with “sufficient” avidity. Does selecting a more functionally diverse array give better immune control? Perhaps low avidity “killers” that “kiss and run” operate optimally to eliminate virus-infected targets, while high avidity “helpers” that stay faithfully in place produce more cytokine. Recent findings indeed suggest that selection of a broad T cell receptor repertoire is characteristic of the initial phase following antigen contact, while continued exposure leads to further cycles of division and the progressive numerical dominance of “best-fit” clonotypes. Here we review recent advances demonstrating a link between T cell repertoire diversity and immunity to infection, and consider the potential mechanisms at play.

Introduction

Each T cell receptor (TCR) $\alpha\beta$ heterodimer imparts specificity for a given peptide+major histocompatibility complex glycoprotein (pMHC) epitope, with the naïve TCR repertoires of mice [1] and men [2] being thought to contain 10^7 or 10^8 unique signatures. This potential for broad reactivity ensures that effective T cell responses can be mounted against the myriad of pathogens encountered in nature. However, while both the diversity of TCR recruitment and the avidity of the TCR/pMHC interaction can vary substantially for different epitopes, just how these two variables factor into the development of optimal T cell effector function and memory is still far from clear. As we seek to evolve improved T cells vaccine and immunotherapy strategies, it is important to develop a better understanding of the rules governing this nexus between TCR repertoire diversity, binding and function.

Molecular basis of TCR diversity

Each TCR chain contains a variable (V) and constant (C) region. The V β -region is a combination of variable (V), diversity (D) and junctional (J) gene segments, whereas V and J gene segments encode the V α -chain [3]. Multiple TCR V α , J α , V β , D β and J β segments within the TCR locus [4] are generated via random splicing of TCR gene segments during T cell development and antigen-specificity is imparted by the hypervariable complementarity-

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determining regions (CDRs) encoded within the V gene segments [5]. While the CDR1 and 2 regions are germline, the CDR3 region is generated after VJ and VDJ gene recombination. Different V gene segment combinations, combinatorial and junctional variation within the CDR3 α and CDR3 β regions [6] and the addition of non-templated nucleotides at the V(D)J junctions [7] all contribute to the diversity observed within the naïve TCR repertoire. While many factors can shape TCR diversity of immune T cell populations [8,9], it is less clear how T cell diversity imparts effective immunity.

TCR diversity and functional heterogeneity within a given repertoire

Activation [10] of naïve T cells requires i) TCR/pMHC ligation (signal 1); ii) co-stimulation (signal 2) and iii) inflammatory cytokines (signal 3). Ideally, these signals are integrated to ensure optimal proliferation and the acquisition of effector function and memory [11-13]. The affinity of an individual binding event translates to avidity as multiple TCR/pMHC engagements mediate the T lymphocyte/antigen presenting cell (APC) interaction. Affinity/avidity is clearly the gatekeeper determining the necessary level of “fitness”, or signaling threshold, for the recruitment and emergence of any given T-cell clone in a particular immune response [11,14]. Intuitively, selection of a diverse TCR repertoire might be thought to enhance functional heterogeneity, with the high avidity T cells being the more potent effectors [15]. But it isn't always that simple.

After influenza A virus infection, the essentially “private”, TCR-diverse and higher avidity D^bPA₂₂₄-specific CD8⁺ cytotoxic T lymphocyte (CTL) population has a greater capacity for inflammatory cytokine production than the more TCR-constrained, substantially “public” D^bNP₃₆₆-specific CTL set [16]. However, analysis of T cells specific for the influenza D^bPB1-F2 epitope suggests that there is no link between TCR diversity and multiple cytokine production [17]. Recent TCRV β repertoire analysis demonstrated no difference in clonotype usage between of single and multiple cytokine producers within both the D^bNP₃₆₆ and D^bPA₂₂₄-specific CTLs (NLG, ST, unpublished data). This suggests that functional quality is not dictated by TCR usage within antigen-specific CTL. Furthermore, mature D^bPA₂₂₄- and D^bNP₃₆₆- specific CTLs have identical profiles of perforin and granzyme mRNA expression, indicating that the acquisition of cytotoxicity is not modulated by differences in TCR repertoire diversity [18,19].

Maturing T cell responses can “evolve” to a state of increased “functional avidity” as determined by the capacity to respond to lower concentrations of peptide [20-22]. The effect has been shown for TCR-diverse endogenous responses [20,21] and for adoptively transferred CD4⁺ [22] and CD8⁺ [21] transgenic T cells. Functional capacity may, in fact, be determined primarily by the extent of T cell division, [23], as heterogeneity of effector phenotype can be characteristic of a single, antigen-specific clone during an infectious process [24•]. Overall, the stochastic nature of T cell functional acquisition looks to be broadly independent of TCR diversity [14,18,25].

Linking TCR diversity and immunity to infection

Given that TCR diversity may not be the key determinant of functional heterogeneity, how important is breadth of repertoire engagement in a given infectious process? The experiment of Messaoudi *et al* provides compelling evidence of a link between TCR diversity and protection from infection [26•]. Herpes Simplex Virus (HSV) infection of C57BL/6J (B6) mice induces a prominent CD8⁺ T-cell response to a 9 aa glycoprotein B (gB) peptide (SSIEFARL) presented equally well by wild-type H2K^b and mutant H2K^{bm8} (4 aa differences) MHC1 alleles. Presumably the gB antigen load would be the same in these two cases but, while the B6 mice were susceptible to HSV infection, the bm8 mutants were resistant. This increased resistance

was related to greater TCR diversity and the selection of higher avidity gB-specific CTLs in the bm8 mice.

Preferential selection of higher avidity TCRs in an immune response

How does the immune system ensure the selection of a diverse, yet high avidity TCR repertoire? Malherbe et al [27••] fixed the TCR β -chain for I-E^k/pigeon cytochrome C peptide (PCC₈₁₋₁₀₄)-specific CD4⁺ T cells, then determined the extent of pre- and post-immune I-E^k/PCC₈₁₋₁₀₄-specific TCR repertoire diversity by analysing the spectrum of CDR3 α sequences utilized by these TCR β -transgenic CD4⁺ T cells. They concluded that there is an initial low threshold of activation permitting the recruitment of both high (best-fit V α) and low (less ideal V α) affinity TCRs into the early stages of the immune response. However, a second threshold favored the continued expansion of clonotypes expressing those TCRs with optimal structural and affinity characteristics, leading to domination of the mature effector response by the higher avidity set.

Direct evidence that high TCR affinity for a given pMHC optimizes sustained T cell expansion to infection has recently been provided by Zhen and colleagues [28••]. Using aa substitutions to modify the wildtype ovalbumin (OVA₂₅₇₋₂₆₄) peptide alters the binding affinity for OT-I TCR transgenic T cells, with resultant differences in the level of activation [29]. Using this system, Zhen et al examined the fate of adoptively transferred OT-I T cells after infection with *Listeria monocytogenes* recombinants expressing either the WT OVA₂₅₇ or mutant peptides. In line with the Malherbe study [27], both low and high affinity TCR-pMHC interactions were able to induce OT-I T cell proliferation, though only high affinity binding could sustain a full T cell response. Interestingly, the lower avidity T cells migrated early into the periphery, raising the possibility that they play a useful part early on. Numerically, though, the evolution of the response overall towards high avidity is a consequence of T cell retention in the lymphoid tissue and prolonged exposure to antigen. Furthermore, while the idea [30,31] that an early “hit” leads to an inexorable program of differentiation from the naïve precursor state may well be valid, both the Malherbe et al and Zahn et al experiments establish that the extent to which any clonotype dominates a primary response is a consequence of continuing antigen exposure and resultant proliferation.

The requirement to reach an avidity threshold ensures that only TCRs with sufficient affinity are recruited by antigen. Furthermore, the selection of the higher avidity T cells for further cycles of proliferation means that they are likely to be the more important players in a fully developed immune response [15,32]. However, if there is indeed progressive selection of best-fit TCRs into the mature immune T cell repertoire, shouldn't antigen-specific TCR diversity inevitably narrow? This effect can be seen for the influenza A virus D^bNP₃₆₆-specific response, where there is initial recruitment of a broad spectrum of (presumably) low avidity CD8⁺ T cells that (while they may persist into memory) remain CD62L^{hi} and never expand [33]. Where such narrowing is not observed, compensatory mechanisms related to CD4 and CD8 co-receptor binding may serve to stabilize some less optimal TCR-pMHC interactions [34] and effectively reduce the activation threshold [35]. The interplay between co-receptor and TCR-pMHC avidity may thus serve to promote greater TCR diversity in antigen-selected TCR repertoires [36].

Increased TCR diversity favors cross-reactivity to similar pMHC structures

The flexibility of TCR CDR regions allows a variety of binding solutions for topographically similar pMHC structures [37•-39]. This plasticity can potentially operate to ensure T cell reactivity to pMHC variants that may emerge as a consequence of virus escape. Infection of rhesus macaques with simian immunodeficiency virus (SIV) induces CD8⁺ T-cell responses specific for peptides derived from the viral Tat (aa 28–35, TTPESANL; denoted TL8) and Gag

(aa 181–189, CTPYDINQM; denoted CM9) proteins, both presented by the MHC class I molecule Mamu-A*01. The CTLs that recognize CM9–Mamu-A*01 exhibits a diverse array of CDR3 β sequences, whereas the TL8–Mamu-A*01-specific set utilizes a conserved CDR3 β motif. The limited TCR diversity within the latter repertoire is associated with the rapid selection of a TL8 escape variant. In contrast, the more diverse CM9–Mamu-A*01-specific response is not subverted in this way [40]. A likely reason for the difference is that the more diverse CM9–Mamu-A*01-specific repertoire has TCRs capable of finding alternate binding solutions for epitope variants as they appear, thus limiting the emergence of escape mutants.

A more extreme example of cross-reactivity is when memory CTLs induced by one infection are recalled after exposure to a second pathogen [41–43]. The breadth of such CTL immunity is clearly dependent on the available TCR repertoire [43], with there being some evidence for heterologous protection against challenge with viruses that have not been encountered previously [42,44]. The selective effect imposed by the second infection can, however, also lead to narrowing of a given memory TCR repertoire and the subsequent emergence of CTL escape mutants following re-infection with the original pathogen [41]. Any benefits of cross-reactive immunity to heterologous infection are thus only likely to be apparent if antigen-specific TCR diversity is maintained.

T cell function and the nature of the APC interaction

Experiments with influenza A viruses in B6 mice have shown that the TCR-diverse, high avidity D^bPA₂₂₄-specific CTLs produce greater levels of IFN- γ , TNF- α and IL-2 than the more TCR-constrained, lower-avidity D^bNP₃₆₆-specific set. However D^bNP₃₆₆ is expressed on the surface of a variety of cell types [45] while D^bPA₂₂₄ is found only on dendritic cells (DCs). Furthermore, time-lapse video microscopy showed that *ex vivo*-isolated D^bNP₃₆₆-specific CTLs elute more quickly from peptide-pulsed target cells [46]. This suggests the possibility that high avidity T cells like the D^bPA₂₂₄-specific set function to produce more cytokine (and promote an appropriate inflammatory environment) as a consequence of prolonged contact with the pMHC on DCs. By contrast, the lower-avidity, “kiss and run” D^bNP₃₆₆-specific CTLs may achieve greater levels of virus-infected target cell elimination as they deliver their lethal “hit”, then move on with enhanced kinetics. An “ideal” TCR repertoire may thus span a range of avidities, ensuring that various functional requirements are fulfilled at different times during an immune response.

Memory T cell generation can occur soon after the initial stage of naïve T cell activation [47,48]. Furthermore, the profile of TCR diversity within the memory T cell pool may indeed be established very early [33]. A recent analysis demonstrated that the generation of effector versus memory T cells can be separated on the basis of differential TCR signaling [49], an effect that could be related to the anatomical positioning of a proliferating “daughter” T cell relative to the APC. This segregation of TCR mediated signals during the antigen-driven response may well be a primary mechanism for ensuring the maintenance of both TCR and functional diversity within the memory T cell repertoire.

Concluding remarks

There is increasing evidence that that TCR diversity within antigen-specific T cell repertoires is important for ensuring effective immune elimination and subsequent protection [26]. Enhanced immunity with greater TCR diversity stems variously from shaping the role of particular T cell clones in the host response, selecting TCRs capable of cross-reactivity and maintaining diversity within the memory T cell compartment. A major question is: how do structural constraints influence TCR repertoire diversity and subsequent immunity? For example, do different TCR clonotypes specific for the same pMHC complex utilize similar

binding solutions, or are there multiple topographical conformations that give the same result? Furthermore, when it comes to recruitment, effector T cell efficacy and the generation of immune memory, is there any functional consequence of emphasizing different TCR-pMHC binding solutions?

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