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Private specificities of heterologous immunity

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Antiviral T-cell responses between individuals that have similar major histocompatibility complex molecules share similarities in epitope hierarchies and T-cell receptor variable gene usage (public specificities), yet the T-cell receptor amino acid sequences differ between individuals (private specificities). The significance of the private specificities of these repertoires is brought about under conditions of heterologous immunity and might have important consequences in anti-viral immunity and immunopathology.

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Current Opinion in Immunology 2006, **18**:331–337

This review comes from a themed issue on
Lymphocyte effector functions
Edited by Stephen Schoenberger

Available online 4th April 2006

0952-7915/$ – see front matter

DOI 10.1016/j.coi.2006.03.002

Introduction

The terms 'private' and 'public' specificities were used originally to describe the antigenic relationships between different MHC molecules and the ability of T cells or antibodies to detect determinants unique (private) to a molecule or cross-reactive (public) between them [1,2]. More recently, this term has been applied to describe the repertoire of antigen-specific T cells, whereby "a public response is identical in all animals and a private response is specific to each individual" [3]. I prefer to expand the use of this terminology to include the hierarchy of epitope-specific T-cell responses in addition to the T-cell repertoire used per epitope-specific response. These become important issues in the field of heterologous immunity.

This review will discuss how private immune responses unique to the individual might play roles in anti-viral immunity and immunopathology.

The uniqueness of T-cell receptor repertoires

The rearrangement of TCR germ-line DNA sequences and the pairing of the α and β TCR molecules create a theoretical possibility of about 10^{15} different T cells [4,5]. This theoretical number is, of course, greatly pruned as T cells pass through the thymus and become positively and negatively selected. Nevertheless, the variations of T-cell receptor (TCR) repertoires among individuals remain immense, considering that their diversities in the mouse and human are reported in the ranges of 10^6–10^7 and 10^7–10^8, respectively [4,6]. In non-immune mice, direct sequencing of splenic T cells with TCR known to be reactive against a mouse class I MHC K^d-restricted human leukocyte antigen (HLA)-CW3 epitope expressed in mouse P-815 cells revealed substantial diversity between the ~200 clones found per mouse [7]. This means that genetically identical mice have non-identical and, in fact, quite different naïve T-cell repertoires poised to be recruited into an antigen-specific immune response.

Analyses of the repertoire between genetically identical mice have indicated similarities in the proportions of T cells that represent different variable (V)β families, and suggestions have been made in human studies that the TCR complement-determining regions (CDR)1 and *2*, which vary between Vβ families, might be involved in selecting these families in an MHC-dependent manner [8,9]. A great level of diversity of the private repertoire is associated with variations in CDR3 length and sequences created by template-independent nucleotides added on by terminal deoxynucleotidyl transferase (TdT). TdT-knockout mice were shown to have only 5–10% of the T-cell diversity of normal mice [10], but their Vα and Vβ public repertoires were similar to that of the wild-type mice [11••]. These mice generate surprisingly good immune responses to viruses, with normal epitope hierarchies and Vβ usage [11••,12], despite the greatly reduced diversity of their repertoires.

Public and private T-cell receptor specificities in anti-viral responses

T-cell responses to viral epitopes occur in a distinct hierarchy for a given virus on a given MHC background. For instance, in the C57BL/6 (MHC of $H2^b$) mouse, the CD8 T-cell response to lymphocytic choriomeningitis virus (LCMV)-encoded epitopes will usually be in a hierarchy of NP396-404 > GP34-41 > GP33-41 > GP276-286 > NP205-212 [13,14••]. Because most LCMV-infected mice show this hierarchy, we can think of this as a public specificity. What governs this hierarchy are issues such as the competition between epitopes for presentation by the MHC, the availability of a non-tolerized repertoire of T cells capable of responding to the epitope, and the competition between T cells binding to domains on the antigen-presenting cells [15]. The private specificities of the repertoire of T cells coming

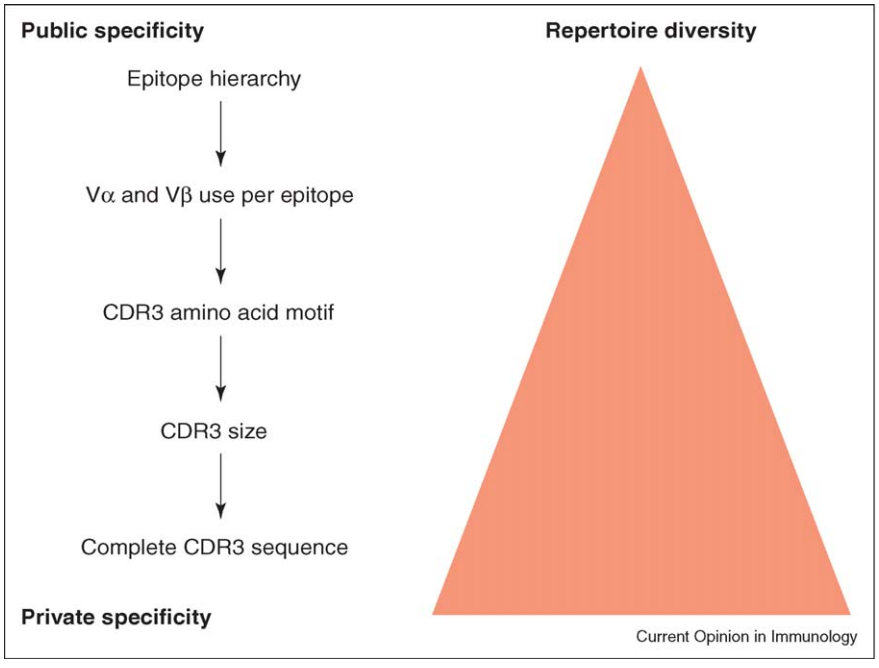
out of the thymus appear to have little impact on this public epitope hierarchy.

The first detailed analyses of TCR sequence diversity were of discrete experimental epitopes of hen egg lysozyme, cytochrome C or human HLA-CW3 presented on mouse cells [3,16,17]. T cells from different mice responding to these epitopes diplayed preferential Vβ TCR usage (public specificity) but different CDR3 lengths and/or amino acid sequences (private specificity), even though there were conserved amino acid motifs in the antigen-binding regions. Similar phenomena have now been found during the analyses of virus-specific T-cell responses [18–22,23•,24,25], which are more complex because of the diversity of epitopes being displayed at any given time. Some epitopes, such as the influenza class I D^b-presented $NP_{366-374}$ epitope, might be more public than others, such as the influenza D^b-$PA_{224-233}$ epitope, in being more likely to induce a limited Vβ repertoire [22,26••,27]. A high diversity in the T-cell response to D^b-$PA_{224–233}$ has been linked to the availability of amino acid side chains; this is not found with the more buried $NP_{366–374}$ epitope [26••]. Even in this case, however, different private responses to either epitope are engendered between mice. In general, it can be stated that epitope hierarchies, Vβ usage and conserved CDR3 motifs tend to be public, but an immune response is very ultimately private because TCR that have different CDR3 amino acid lengths and sequences are used in the epitope-specific response of each individual (Figure 1).

This individual variation in TCR repertoire could be explained either by the differences in TCR repertoires coming out of the thymus and entering the peripheral T-cell pool or by the random stochastic process by which an antigen-specific T cell encounters its antigen *in vivo*, perhaps causing it to become clonally dominant if the encounter occurs early in infection. Experiments showed that TCR repertoires generated in response to K^d-expressed CW3 differed even when naïve T cells from one mouse were transferred into two recipients [28]. Similarly, adoptive transfer of pooled naïve T cell populations into five T cell-knockout mice revealed great diversity of the repertoire after LCMV infection [21]. These experiments suggest that both explanations for repertoire diversity might be correct, although diversity of cells emanating from the thymus probably explains most of it. Adoptive transfers of memory T cell populations that contain expanded clones of T cells into several recipients, however, result in similar responses between recipients [14••].

Most studies indicate that the TCR repertoires of epitope-specific T cells are similar in different anatomical sites within an individual, that they are similar at the peak of the immune response and the resting memory state, and that re-challenge with homologous antigen only modestly focuses the repertoire [16,18–22,24,27]. Most studies also suggest that the private specificity of the T cell repertoire plays relatively little role in the generation of epitope hierarchies and in the immune control and

Figure 1



T-cell diversity among MHC-matched immunologically naïve hosts after viral infection. This figure shows that naïve hosts have little diversity in epitope hierarchies but increase in their diversities progressively, to the point at which the TCR CDR3 sequences can be highly variable between hosts.

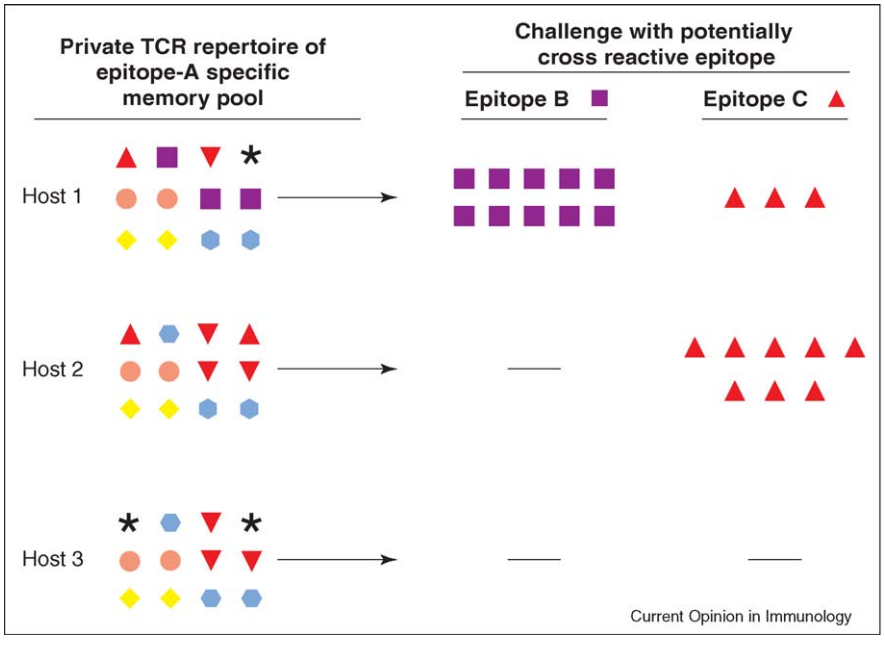
immunopathology of viral infections in immunologically naïve mice, given the reproducibility in experiments with a virus such as LCMV. All things change, however, in the context of heterologous immunity, in which the impact of the private specificities comes to the forefront.

T cell cross-reactivity and heterologous immunity

The term heterologous immunity has been used to refer to the influence that immune memory to previously encountered pathogens has on immunity to and pathogenesis of subsequent infections with unrelated pathogens [29]. In some cases this is regulated by T cells cross-reactive between the two pathogens, and many examples of such cross-reactivity now exist [30]. Because of the elevated frequencies of antigen-specific memory T cells and their elevated activation state, infection of a host with a virus that encodes an epitope cross-reactive with that memory pool might recruit those T cells into a vigorous immune response that could become immunodominant and suppress responses to other epitopes [31–33]. This has been clearly shown between LCMV and Pichinde virus, which encode cross-reactive K^b-restricted $NP_{205–212}$ conserved epitopes that share 6 of 8 amino acids. Thus, heterologous immunity affects immunodominance and the public hierarchies of epitope-specific responses during viral infections. Such cross-reactive dominant responses might provide good protective immunity, but some responses could be directed against epitopes not suitable for control of viral infections (such as epitopes that are weakly presented, cross-presented to uninfected cells, or expressed late in infection), and might tip the balance from protective immunity to immunopathology.

A cross-reactive epitope that does not have 100% sequence identity is likely to stimulate the proliferation of only a subset of the T-cell repertoire generated against the immunizing epitope [34,35•] (Figure 2). Because the TCR repertoires of each host will be different, it is here that the impact of private specificity comes into bearing. The CDR3 of TCR often have amino acid motifs that enable a TCR to interact with a specific peptide–MHC, but other stochastically positioned amino acids unimportant for recognition of the first-encountered epitope might play a role in interacting with the second epitope. Depending on the variation of the private TCR CDR3 sequences, an epitope-specific T-cell pool in one individual might be more or less cross-reactive with a second epitope than a T-cell pool specific to the original epitope in another individual (Figure 2). In fact, we have noticed that, in the case of the highly cross-reactive epitopes between LCMV and Pichinde virus, sequential infections elicit major differences in the magnitude of the cross-reactive response between mice, and the epitope-specific responses are narrow oligoclonal responses that differ substantially between mice [35•]. This all means that

Figure 2



Selective expansion of a subset of an epitope-specific repertoire by a cross-reactive epitope. The symbols represent the differences between private epitope-specific repertoires within three different hosts and how cross-reactive epitopes might or might not induce a profound expansion of a subset of that repertoire. Host 1 has memory cells cross-reactive with epitopes B and C, host 2 has memory cells only cross-reactive with epitope C, and host 3 has memory cells cross-reactive with neither B nor C. Although hosts 1, 2 and 3 generate good memory to epitope A, because of the nature of the private specificities of their TCR repertoires, they might respond very differently when infected with a cross-reactive pathogen.

the private specificity of memory pools might dictate the nature of a cross-reactive response.

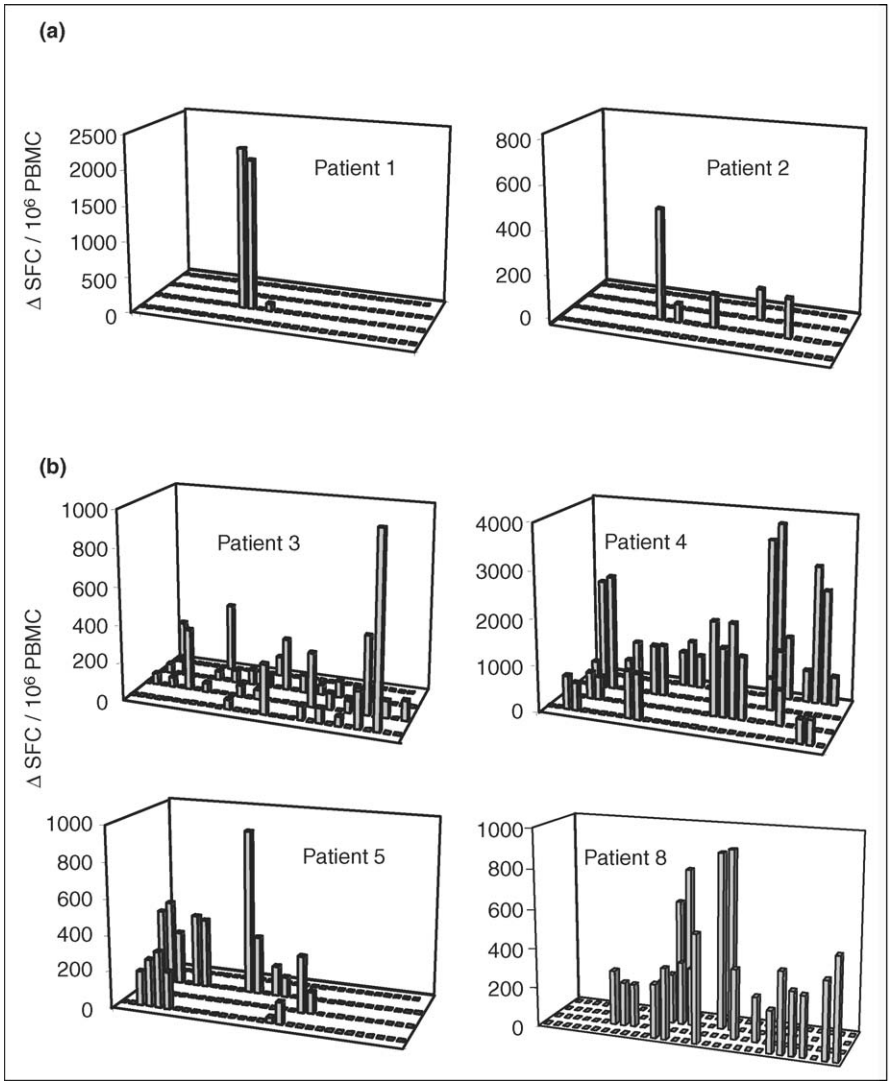
Impact of private specificities in heterologous immunity

In the past year three studies have demonstrated the impact of private specificities of T-cell responses on heterologous immunity [14••,36••,37••,38]. These have been performed in mice having cross-reactive responses between LCMV and vaccinia virus (VV), and in humans having cross-reactive responses between influenza virus and hepatitis C virus (HCV) or Epstein-Barr virus (EBV).

Heterologous immunity between lymphocytic choriomeningitis virus and vaccinia virus

In C57BL/6 mice, a history of LCMV infection provides a level of protective immunity to VV by reducing organ titers by 1–2 logs 3–4 days post-infection. It also enhances immunopathology, in that intraperitoneally challenged mice develop panniculitis and fatty necrosis in visceral fat similar to human erythema nodosum, and intranasally challenged mice develop bronchiolitis obliterans similar to the human disease of unknown etiology [39–41]. In both cases the affected tissue is infiltrated by LCMV-specific T cells.

Figure 3



Diversity of T-cell responses from **(a)** severe course or **(b)** mild course patients undergoing acute HCV infection. A severe course of disease was monitored by rapidly rising bilirubin, prolonged prothrombin time, and elevated serum glutamic pyruvic transaminase (ALT). Plots show ELISPOT interferon γ responses of T cells stimulated against overlapping peptides that cover the entire HCV genome. Patients 3, 4, 5 and 8, presented in (b), had T-cell responses specific to a wide variety of HCV peptides displayed in these grids. In contrast, patients 1 and 2 (a) had dominant responses to a peptide encompassing the HCV/influenza virus cross-reactive epitope [36••]. Abbreviations: ELISPOT, enzyme-linked immunosorbent assay; PBMC, peripheral blood mononuclear cells; SFC, spot-forming cells. Reproduced from The Journal of Experimental Medicine 2005, vol. 201, pp. 675–680, by copyright permission of the Rockefeller University Press [36••].

In an attempt to determine the nature of cross-reactivity between LCMV and VV, it was first noticed that VV infection sometimes expanded T cells directed at one LCMV epitope, but in other mice the response was directed against another epitope. Adoptive transfers of splenocytes from different LCMV-immune donor mice into three recipients revealed similar specificities in each of the recipients after VV challenge [14••]. This means that the private specificity of the LCMV-induced immune response in an individual mouse dictated the pattern of cross-reactivity on VV challenge and that there were complex patterns of cross-reactivities between different viral epitopes, a conclusion supported by staining with tetramers specific for LCMV and VV epitopes. In addition, the magnitude of expansion of T cells specific to the VV-specific K^b-restricted cross-reactive epitope $A11R_{198–205}$ varied with the private specificity of the LCMV-immune T-cell pool [14••].

Heterologous immunity between influenza virus and Epstein-Barr virus

Acute infectious mononucleosis (AIM) is an EBV-induced disease associated with a dramatic expansion of CD8 T cells. It presents as a mild disease in children but a more severe disease in young adults; the increased severity is thought to be caused by the immune response rather than increased viral load [42]. Cross-reactive T-cell responses were demonstrated between the HLA-A2-restricted highly conserved immunodominant influenza virus epitope $M1_{58–66}$ and an immunodominant EBV epitope $BMLF1_{280–288}$, which have only 3 of 9 amino acids in common [30,37••]. 5 of 8 HLA-A2 patients with AIM had activated M1-specific responses, and double tetramer staining revealed substantial levels of the cross-reactive T cells. This led to the hypothesis that cross-reactive T cells participate in the pathogenesis of AIM. Of note is that, even though all patients were presumed to have had influenza, not all patients had these cross-reactive responses, suggesting a private specificity phenomenon [37••].

Heterologous immunity between influenza virus and hepatitis C virus

The pathogenesis of HCV is highly variable between individuals, with some efficiently clearing the virus, others developing long-lasting persistent infections, and, rarely, others getting severe fulminant hepatitis [43]. This variation in disease course leads one to hypothesize that heterologous immunity might influence the course of the disease. Notably, a strong cross-reactive T-cell response has been described between the HLA-A2-restricted HCV epitope $NS3_{1073–1081}$ and the influenza virus NA $_{231–239}$ epitope, which share 7 of 9 amino acids [44]. Studies analyzing the breadth of T-cell responses of HCV patients noted that 2 of 8 patients generated overwhelming immunodominant responses to the cross-reactive epitope, and that those two patients developed severe hepatitis, whereas those with a broader response had less severe symptomatology [36••] (Figure 3). Because all the patients should have encountered influenza virus previously in their lifetimes but only one quarter developed such immunodominant responses, there might be an important private specificity phenomenon here.

Conclusions

Results in the past year have added a new twist to the concept of heterologous immunity. Depending on the nature of the cross-reactivity between epitopes and the presumed private specificity of the memory T-cell repertoire directed at those epitopes, a dominant cross-reactive response might or might not be elicited, and the epitope specificities of the cross-reactive response and immunodominant epitope hierarchies might change depending on the individual. This could manifest itself in different types of disease states between individuals. Thus, in our attempts to explain variations in the pathogenesis of viral infections in humans, we need to look not only at factors such as an individual's genetics, physiological state and infection history, but also at the private specificities of that individual's unique T-cell repertoire.

Acknowledgements

This work was supported by US National Institutes of Health (NIH) research grant AR35506. The views are those of the author and not the official position of the NIH. I thank Keith Daniels for the art work.

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