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Immunodominant viral peptides as determinants of cross-reactivity in the immune system — Can we develop wide spectrum viral vaccines? ☆

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Summary When we look back to Edward Jenner vaccination of a young man in 1796, we cannot help thinking that he was both lucky and crazy. Crazy because he decided to test in a human being a hypothesis based mainly in the traditional belief that people who had acquired cowpox from the udders of a cow were thereafter resistant to smallpox, a quite devastating disease, and lucky because (even considering that he did not know this at that time) he succeeded to induce protection against a pathogen through the induction of an immune response directed against a different agent. Not only was he able to protect the young man but he took the first step towards the development of a vast new field, vaccination. It is acceptable to say that Jenner was lucky because he succeeded in promoting protection against smallpox using a cowpox virus and this induction of protection in a cross-reactive way is believed to be quite rare. Nevertheless, more and more examples of cross-reactive immune responses are being described and we are beginning to admit that cross-reactivity is far more common and important than we used to think. Here we review cross-reactivity in the immune system and the plasticity of T cell recognition. Based on the existence of T cell receptor promiscuous recognition and cross-recognition of conserved viral immunodominant epitopes, we propose two approaches to develop wide spectrum viral vaccines. The first one is based on the identification, characterization, and cloning of immunodominant viral epitopes able to stimulate responses against different viruses. The produced peptides could then be purified and serve as a basis for vaccine therapies. A second strategy is based on the identification of conserved patterns in immunodominant viral peptides and the production of synthetic peptides containing the amino acid residues necessary for MHC anchoring and TCR contact. Although we are still far from a complete knowledge of the cross-reactivity phenomenon in the immune system, the analysis of immunodominant viral epitopes and the identification of particular ''viral patterns'' seems to be important steps towards the development of wide spectrum viral vaccines.

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Introduction

The human immune system has developed, throughout its evolution, different mechanisms to eliminate pathogenic organisms. Pathogens, in

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turn, have developed strategies to evade our defense mechanisms. Some of the interaction mechanisms between the immune system and pathogens are already well understood. For viral systems, however, the subject is not fully elucidated, mainly due to the highly mutable nature of viruses, which requires the development of specialized and complex defense mechanisms.

Many cells of the immune system are involved in the eradication of viral infections. We will give special attention to the interactions between cells that express major histocompatibility complex (MHC) class I molecules (all the nucleated cells) and cytotoxic $CD8^+$ T lymphocytes (CTLs).

When an MHCI-expressing cell is infected by a virus, it starts producing proteins necessary to viral assembly. Part of these proteins is, however, proteolytically degraded in the proteasomes, along with other cytosolic self-proteins or even proteins provenient from intracellular bacteria that have been also ubiquitinated. This degradation process generates peptides 6—30 amino acids (aa) long that may, potentially, bind to the MHC class I molecule peptidic cleft, in the endoplasmic reticulum, being transported to the cell surface. These peptides have little variation in size, presenting normally 8—12 amino acids. The peptide size restriction is due to the nature of the MHC I peptidic cleft, which presents closed extremities, contrasting to the peptidic cleft of MHC class II molecules which can accommodate longer sequences (up to 30 aa).

Imagine that a given viral protein possesses 200 amino acids and that its proteolysis generates, in average, peptides with 10 aa (it must be emphasized that fission does not occur, necessarily, at 10 aa from the initial extremity, but that random cuts in any part of the protein generate peptides of different sizes). The number of sequences yielded, in such case, would reach some hundreds. Considering that the exemplified protein size is relatively small and considering the classical idea that each CD8+ T cell recognizes only one peptide, the repertoire of memory T cells would have to be larger that 10^{12}, the total number of lymphocytes in human beings, to be efficient [1]. Therefore, the recognition of peptidic sequences must involve mechanisms with a certain plasticity and adaptability, without, however, loss of specificity. This would allow the immune cell repertoire to be shaped according to ongoing experiences leading to the establishment of memory, but at the same time, it would allow the maintenance of a source of naive, inexperienced cells.

We will discuss here some mechanisms that could indicate events that bypass the problem of the size limitation of the immune system and, at the same time, could confer it a powerful resource for viral recognition. Most of these mechanisms involve cross-reactivity.

Cross-reactivity

The capacity of a T lymphocyte to recognize non-related peptides derived from the same virus, or even peptides from heterologous viruses, will be defined here as cross-reactivity [2,3]. This phenomenon is mainly observed in cytotoxic T lymphocytes, even though it also occurs in T helper cells [4]. Several examples of cross-reactivity between heterologous viruses have already been described and some of them will be presented throughout the text.

Brehm et al. [5] demonstrated that the sensitization with a subdominant epitope of the lymphocytic choriomeningitis virus (LCMV) elicits strong immune response against an heterologous subdominant epitope of the pichinde virus (PV). It is important to note that the PV peptide which elicited the cross-reactivity shared six out of eight amino acids with the one used to sensitize the cells. In that case, infection with an heterologous virus stimulated a strong T cell immunodominant response to an epitope that was previously weak and subdominant, indicating that not only the hierarchy of virus-specific T cells can be more malleable than formerly imagined, but also that the hierarchy of immunodominance can be deeply affected by previous encounters with heterologous pathogens.

Another interesting work involved a panel of four heterologous viruses: LCMV, PV, vaccinia virus (VV) and murine cytomegalovirus (mCMV). This study evidenced that memory T cells primed by a given virus may alter the host immune response to a second unrelated virus. Thus, cross-reactivity was observed between those viruses, mainly between LCMV and PV, and between LCMV and VV. It was also demonstrated that previous immunization with one of those viruses, in some cases, enhanced the clearance of a second unrelated virus, early in infection, although the sequence of viral infection was important and cross-protection was not necessarily reciprocal [6].

In the work of Wedemeyer et al. [1], the presence of specific CD8+ T cells directed to one immunodominant epitope of the hepatitis C virus (HCV) among blood donors that did not present any history of infection by HCV or hepatitis B virus (HBV), led to an inquiry that revealed that those patients had been cross-sensitized by a previous encounter with influenza A virus (IVA). The cross-response occurred against one endogenously pro-

cessed epitope of the IV neuraminidase (IV_{NA-231}), which is conserved among influenza viruses, being normally included in vaccines, and an HCV immunodominant viral determinant called $HCV_{NS3-1073}$, which is an HLA-A2 determinant frequently recognized during acute HCV infection. In the previous example, the degree of similarity between the sequences of both epitopes, which share seven out of nine amino acids, seems to be quite important. Additionally, both peptides present conserved aa in residues 2 and 9, the critical residues for binding to the HLA-A2 molecule. Although they differ in two aa, these non-identical amino acids belong to the same chemical group and share certain physicochemical characteristics.

Several examples of cross-reactivity involving the influenza virus have already been reported. This is, to a certain extent, an expected fact since any given human immune system is challenged by this virus several times throughout life. Consequently, memory cells for many epitopes, from different influenza strains, must be abundant in the T cell repertoire of any human being.

In 1989, Shimojo et al. [7] observed that a rotavirus-derived peptide could sensitize HLA-A2.1+ targets, inducing their lysis by CTLs specific to a IV-derived matrix peptide. One variant of this IV peptide, the FLU-M1:58—66, presented cross-reactivity with an HIV-I epitope. Cells stimulated in vitro with FLU-M1 were capable of lyse not only cells marked with the IV epitope but also cells presenting the HIV epitope [8]. It is interesting to point out that this observation was done in peripheral blood mononuclear cells from both HIV-infected and uninfected individuals, suggesting that, in individuals vaccinated against influenza, the response generated against the IV matrix protein could direct a specific immune response to an HIV epitope. It is known that the IV matrix protein and the HIV capsid and matrix proteins present notable structural similarities, mainly in the three-dimensional structure of the proteins rather than homology in the amino acid sequence. Interestingly, both virus proteins have similar functions in their assembly, mediating the encapsidation of the ribonucleoprotein complex by the viral membrane [9]. Another work demonstrated the existence of cross-reactivity in the immune responses directed to japanese encephalitis and dengue viruses [10].

Among phylogenetically related viruses there are several examples of cross-recognition, such as the occurrence of cross-recognition to different peptides from the same subtype of influenza virus A (IVA) [11], or among epitopes from different subtypes of IVA [12], although cross-reaction between viruses with widely divergent primary amino acid sequences (HIV-1 and HIV-2, for instance) seems also to be common [13].

T cell receptor promiscuous recognition

Much of the cross-reactivity phenomenon involves the degenerated capacity for antigen recognition of the T cell receptor (TCR). The TCR consists of an heterodimeric structure formed by an α chain and a β chain or, alternatively, a γ and a δ chain. Within each one of these chains, there are three hypervariable sites known as complementary determining regions (CDRs), which protrude as loops from the TCR and directly contact sites on the peptide and MHC molecule [14].

The classical view of a monogamous relationship between the TCR of a given lymphocyte and the corresponding MHC-peptide (MHC-pep) complex has been wearing. As previously mentioned, the number of MHC-pep complexes that could be generated exceeds that of T cells in the repertoire of an individual. Specifically, this limitation is due to spatial and/or numerical restrictions on the mature T cell pool, rather than the number of possible TCR rearrangements. The size of the potential TCR repertoire is estimated in 10^{15}, considering all gene segment rearrangements and the imprecise junctions generated by insertions and deletions in the N terminal regions. This number is greater than the theoretical number for different nonamer peptides that could be generated, which equals 20^9 [15]. It is logical that the repertoire full combinatorial potential cannot be exhausted in humans or other animals, even if there were a mechanism ensuring that any TCR is produced only once in a given individual.

Thus, cross-reactivity is necessary for T cell receptors. Such wide spectrum cells can be activated by a primary peptide and also by closely related peptides, or even by peptides that present a certain homology with the required sequence. The TCR flexibility is exhibited at different levels, influencing the positive selection of immature thymocytes as well as the immune response to heterologous antigens, in peripheral mature T cells [15].

Considering that, during an immune response, it is expected that multiple T cell clones recognize the same MHC-pep complex and considering that the number of potential antigens exceeds that of available T cells, it can be suggested that a high degree of cross-reactivity is an intrinsic and necessary property for an efficient immune system. A mathematical model supports this idea, predicting that a single TCR may be able to interact with over one million different peptides [16]. The CDR3 loops of

the TCR are subject to significant conformational alterations to accommodate the three-dimensional structure of the MHC-pep complex surface. The natural TCR flexibility allows it to be promiscuous in peptide recognition, making it inherently able for cross-recognition [14].

It can be argued that not all possible peptides will naturally occur and that, among them, some will associate with MHC molecules while others will not. Even so, the number of MHC-pep complexes effectively formed is extremely high. Nevertheless, we must consider that not all the MHC-pep complexes formed will trigger clonal expansion, memory CTLs reactivation and infected cell lysis.

Another level in the antigen recognition concerns the MHC. Although the classical view dictates that the majority of antigenic peptides could be recognized in the context of only one or a few alleles of the MHC, nowadays it has been observed that T cell determinants can be recognized in the context of a variety of class II alleles [17], although the structural basis for this promiscuous recognition is not yet understood.

Implications of cross-reactivity in the available T cell repertoire

Brehm et al. [18], through the infection of mice, obtained specific CTLs for LCMV-derived peptides which also recognized allogeneic antigens. These allospecific cells generated in response to the viral infection have been kept in high frequencies in the memory cell compartment, indicating that allospecific CD8+ memory T cells can develop as a consequence of viral infection. In fact, mice previously infected with LCMV were refractory to the tolerance induction to skin allogeneic graft. The susceptibility to tolerance induction is influenced by the immunological history of the individual, i.e., individuals that have suffered multiple viral infections tend to be more refractory to tolerance induction than those who have had less infections. Such observation can have some implications in the transplant research field [19].

Also, previous immunity to a given virus can significantly improve the clearance of a second, nonrelated virus, in initial stages of the infection, when specific high affinity T cells directed against this second virus (generated by the stimulation of naïve T cells) were not yet available. Thus, the task of reducing infection spreading can be delegated to cross-reactive cells and the organism will gain time to assemble a more specific artillery. The idea that cross-reactive T cells lead to a low affinity response to heterologous epitopes generated the argument that this could cause deleterious effects to the host, who would lack an acute, virus-specific immune response for some types of viral infections. In fact, some works have verified that such situation is possible and can be used by viruses as an extra evasion mechanism. It was observed that human papillomavirus type 16 (HPV16)-infected individuals that had developed cervical cancer presented an almost complete absence of specific T lymphocytes directed to the oncoprotein (HPV16) $E7_{11-19(20)}$ epitope. Cross-reactivity between this epitope and a coronavirus epitope called $NS2_{52-60}$ was identified. It was proposed that frequent contacts with a virus could lead to an ''exhaustion'' of the T cell repertoire, which could lead to an inefficient CTL response. Moreover, this same HPV epitope presented considerable sequence homology with peptides from diverse organisms, including some sequences from self-peptides, providing support for the suggestion of toleration of the immune system [20]. Another strategy used by viruses to evade the immune system is exemplified by the murine cytomegalovirus (MCMV), which codes for an evasion immune protein (m152/gp40). This protein prevents the presentation of an immunodominant peptide, provenient from an antiapoptotic protein (M45), in pathologically relevant tissues. Thus, this peptide stimulates a CD8+ long-term response, but the target is not present in the tissues of interest [21].

A possible role for the plasticity of T cell recognition in the development of human immunity is supported by De Silva-Udawatta et al. [22]. Human T cell clones were generated against two autoantigens which are frequent targets of autoantibodies and T cells in the same lupus patient. Interestingly, the TCRs from all isolated clones had substantial sequence homology in their CDR3 region 3. Cloning of the TCR α and β chains from these cells, in a TCR-negative human cell line, and a subsequent analysis of interaction between the TCR and the antigenic peptides revealed TCR stimulation by both peptides, evidencing a degeneration or plasticity in the recognition of these lupus autoantigens by the T cell receptor.

Memory, in the immune system, is also affected by cross-reactivity. The immunological history of an individual will constantly shape the T cell repertoire and, consequently, affect the induction of cells in future viral infections. Memory cells are not isolated in the immune system but participate in an interactive network, which is continuously evolving in such a way that the any immune response modifies the frequency, distribution and activity of all other components of the immune system [23]. Finally, if it was previously thought that

memory T cells were present in relatively low frequency and were essentially resting cells, recent studies have demonstrated that virus-specific CTLs were kept in high frequencies during the lifespan of a mice that had been infected by LCMV, PV or VV. In addition, a subpopulation of those memory T cells consisted of cytolytically active circulating cells, expressing IL-2 receptors and high levels of adhesion molecules, which is in agreement with a plastic and interconnected immune system [6].

How does a virus reveal us its identity?

Considering the previous discussion, and focusing specifically in viral immunodeterminants, some questions arise. If the same peptide can, potentially, trigger either a strong immune response or a barely detectable response, how can we talk about immunodominant peptides? In other words, how can the immune system detect a virus? Beyond the need for costimulation, it seems that viral immunodominant peptides share some characteristics.

Joshi et al. [17] studied cross-reactivity of three promiscuous epitopes of T helper cells (linked to MHC class II), which did not show strong sequence homology and were of distinct origins. The sequences seemed totally not related. A more careful analysis, however, revealed some structural similarities, such as the presence of positively charged residues in the middle of their sequences.

The same work comments that few lateral chains from the amino acids of the peptide concentrate the focus of the TCR action. Moreover, the same TCR can accommodate peptide sequences with different lateral chains, depending on the size and chemical properties of the TCR contact surface.

In addition, a study with an Epstein-Barr virus immunodominant epitope that represents the main target for CTLs identified that only 3 out of 9 amino acids of the peptide possessed crucial function for T cell recognition. Two of those amino acids were anchorage residues and occupied positions 2 and 9, and the residue in position 4 was responsible for making contact with the TCR. Polyalanine analogues that share these 3 amino acids were capable of inducing reactivation and clonal expansion of specific CTLs for the wild-type epitope, indicating that a simple but specific amino acid residue is sufficient to productively interact with the TCR. Not only was the original amino acid (aspartic acid) at position 4 capable of inducing reactivation of specific CTLs, but also the glutamic acid or glutamine, all of them presenting a carbonylic group on the side chain. Such peptides, however, have failed to trigger the cytolytic mechanisms, demonstrating the existence of different requirements in TCR stimulation. Thus, different interactions must induce reactivation of memory CTLs and unchain the cytotoxic mechanisms [24].

We can suggest that, even though there is a need for co-stimulation, some factors really characterize some epitopes as viral sequences and that these ''sequences'' will probably not be represented in higher organisms, otherwise we would observe a high incidence of autoimmune diseases. However, in some cases, viral epitopes present considerable similarities to self peptides and can be involved in the pathogenesis of autoimmune diseases. Epidemiologic evidences alert that infections frequently precede autoimmune reactions, moreover, variant epitopes of viral origin may act as antagonists of their own CTLs, by possessing the anchor residues but not the contact residue.

How can we use cross-reactivity to develop wide spectrum viral vaccines?

Considering the phenomena previously discussed, we can propose at least two major strategies to develop wide spectrum viral vaccines. The first one is based on the identification, characterization, and cloning of immunodominant viral epitopes able to stimulate responses against different virus involved in frequent human diseases. The produced peptides could then be purified and serve as a basis for vaccine therapies. As previously mentioned, a number of peptide candidates fits this initial criteria of cross-reactivity induction, making this first step easy and feasible. After the identification of this potentially useful peptides, several admixtures could be elaborated, aiming at inducing protection to different virus-induced diseases. Certainly, the administration of such a peptide pool should be associated to adequate immune stimuli (meaning the inflammatory/infectious context necessary to induce immune responses) in order to enhance the probability of immune response stimulation and long term protection.

A second strategy is potentially more powerful than the first one, but also demands more time and studies to become a reality. It starts from the identification of patterns (in the amino acid sequence or in the biochemical properties) in immunodominant viral peptides (such as conserved amino acids in specific residues) that are capable to induce immune response against a broad range of different organisms. The deduced conserved amino acid sequences (or biochemical properties)

should be used for the production of synthetic peptides containing the amino acid residues necessary for MHC anchoring and TCR contact. Except for these conserved residues, these synthetic peptides could be filled with amino acids with few or none lateral chains (that could interfere with the MHC/TCR contact). Thus, a priori, a limited number of highly conserved and immunogenic peptides could be enough to induce protection, by means of cross-reactivity, against a variety of virus.

Nevertheless, a series of technical problems surround the identification of conserved viral immunodominant peptides. Obviously, the existence of a ''golden sequence'' containing the elements necessary to stimulate immune responses against all kinds of virus is highly improbable, although the identification of consensus sequences representing different viral groups is a concrete possibility. Also, different HLA alleles require different peptides as anchor motifs and this variability should also be considered during peptide screenings. It is important to point out that sometimes viral peptides are associated to the development of autoimmunity and, consequently, it will always be necessary to take into account the cross-reactive phenomenon as a whole and not only as a characteristic of immune responses against pathogens. Conversely, a potential application to conserved viral epitopes includes tolerance induction against peptides involved in autoimmune diseases. As discussed, these features do not invalidate the potential of immunodominant viral peptides as inducers of long term immune responses but points out the need of a deep knowledge of cross-reactivity phenomena.

Both vaccination approaches previously proposed have as an advantage, the use of single peptides instead of complex viral particles, when compared to conventional vaccine strategies. This is extremely relevant when organisms such as HCV or HIV are the therapy targets. Besides, if relevant conserved features in immunodominant peptides could be identified and associated to specific viral groups (a pool of peptides that confer protection against different IV lineages, for instance), the vaccine could be directed to this viral group, with minimal interference in the remaining T cell pool. Interestingly, as immunodominance hierarchy is affected by previous encounter with other epitopes, also subdominant epitopes could be envisaged as putative candidates to vaccine development. Thus, the analysis of immunodominant viral epitopes in search of particular features and the subsequent use of these features to the development of synthetic peptides with a ''viral pattern'' seems to be interesting steps towards the development of wide spectrum viral vaccines.

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References

[1] Wedemeyer H, Mizukoshi E, Davis AR, Bennink JR, Rehermann B. Cross-reactivity between hepatitis C virus and influenza A virus determinant-specific cytotoxic T cells. J Virol 2001;75:11392–400.

[2] Williams OM, Hart KW, Wang EC, Gelder CM. Analysis of CD4 (+) T-cell responses to human papillomavirus (HPV) type 11 L1 in healthy adults reveals a high degree of responsiveness and cross-reactivity with other HPV types. J Virol 2002;76:7418–29.

[3] Snyder JT, Belyakov IM, Dzutsev A, Lemonnier F, Berzofsky JA. Protection against lethal vaccinia virus challenge in HLA-A2 transgenic mice by immunization with a single CD8+ T-cell peptide epitope of vaccinia and variola viruses. J Virol 2004;78:7052–60.

[4] Selin LK, Nahill SR, Welsh RM. Cross-reactivities in memory cytotoxic T lymphocyte recognition of heterologous viruses. J Exp Med 1994;179:1933–43.

[5] Brehm MA, Pinto AK, Daniels KA, Schneck JP, Welsh RM, Selin LK. T cell immunodominance and maintenance of memory regulated by unexpectedly cross-reactive pathogens. Nat Immunol 2002;3:627–34.

[6] Selin LK, Varga SM, Wong IC, Welsh RM. Protective heterologous antiviral immunity and enhanced immunopathogenesis mediated by memory T cell populations. J Exp Med 1998;188:1705–15.

[7] Shimojo N, Maloy WL, Anderson RW, Biddison WE, Coligan JE. Specificity of peptide binding by the HLA-A2.1 molecule. J Immunol 1989;143:2939–47.

[8] Acierno PM, Newton DA, Brown EA, Maes LA, Baatz JE, Gattoni-Celli S. Cross-reactivity between HLA-A2-restricted FLU-MI: 58-66 and HIV p17 GAG: 77–85 epitopes in HIV-infected and uninfected individuals. J Transl Med 2003;1:3.

[9] Harris A, Sha B, Luo M. Structural similarities between influenza virus matrix protein M1 and human immunodeficiency virus matrix and capsid proteins: an evolutionary link between negative-stranded RNA viruses and retroviruses. J Gen Virol 1999;80:863–9.

[10] Yamada K, Takasaki T, Nawa M, Yabe S, Kurane I. Antibody responses determined for Japanese dengue fever patients by neutralization and hemagglutination inhibition assays demonstrate cross-reactivity between dengue and Japanese encephalitis viruses. Clin Diagn Lab Immunol 2003;10:725–8.

[11] Belz GT, Xie W, Doherty PC. Diversity of epitope and citokine profiles for primary and secondary influenza A virus-specific CD8+ T cell responses. J Immunol 2001;166:4627–33.

[12] Haanen JBAG, Wolkers MC, Kruisbeek AM, Schumacher TNM. Selective expansion of cross-reactive CD8+ memory T cells by viral variants. J Exp Med 1999;190:1319–28.

[13] Bertoletti A, Cham F, McAdam S, et al. Cytotoxic T cells from human immunodeficiency virus type 2-infected patients frequently cross-react with different human immunodeficiency type I clades. J Virol 1998;72:2439–48.

[14] Brehm MA, Selin LK, Welsh RM. CD8+ T cell responses to viral infections in sequence. Cell Microbiol 2004;6:411—21.
[15] Regner M. Cross-reactivity in T-cell antigen recognition. Immunol Cell Biol 2001;79:91—100.
[16] Mason D. A very high level of crossreactivity is an essential feature of the T-cell receptor. Immunol Today 1998;19: 395—404.
[17] Joshi SK, Suresh PR, Chauhan VS. Flexibility in MHC and TCR recognition: degenerate specificity at the T cell level in the recognition of promiscuous Th epitopes exhibiting no primary sequence homology. J Immunol 2001;166: 6693—703.
[18] Brehm MA, Markees TG, Daniels KA, Greiner DL, Rossini AA, Welsh RM. Direct visualization of cross-reactive effector and memory allo-specific CD8 T cells generated in response to viral infections. J Immunol 2003;170:4077—86.
[19] Adams AB, Williams MA, Jones TR, et al. Heterologous immunity provides a potent barrier to transplantation tolerance. J Clin Invest 2003;111:1887—95.
[20] Nilges K, Höhn H, Pilch H, et al. Human papillomavirus type 16 E7 peptide-directed CD8+ T cells from patients with cervical cancer are cross-reactive with the coronavirus NS2 protein. J Virol 2003;77:5464—74.
[21] Holtappels R, Podlech J, Pahl-Seibert MF, et al. Cytomegalovirus misleads its host by priming of CD8 T cells specific for an epitope not presented in infected tissues. J Exp Med 2004;199:131—6.
[22] De Silva-Udawatta M, Kumar SR, Greidinger EL, Hoffman RW. Cloned human TCR from patients with autoimmune disease can respond to two structurally distinct autoantigens. J Immunol 2004;172:3940—7.
[23] Selin LK, Welsh RM. Plasticity of T cell memory responses to viruses. Immunity 2004;20:5—16.
[24] Reali E, Guerrini R, Marastoni M, et al. A single specific amino acid residue in peptide antigens is sufficient to activate memory CTL: potential role of cross-reactive peptides in memory T cell maintenance. J Immunol 1999;162:106—13.