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Antigen processing and presentation in HIV infection

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Abstract

The presentation of virus-derived peptides by MHC molecules constitutes the earliest signals for immune recognition by T cells. In HIV infection, immune responses elicited during infection do not enable to clear infection and correlates of immune protection are not well defined. Here we review features of antigen processing and presentation specific to HIV, analyze how HIV has adapted to the antigen processing machinery and discuss how advances in biochemical and computational protein degradation analyses and in immunopeptidome definition may help identify targets for efficient immune clearance and vaccine immunogen design.

Keywords

HIV; immunopeptidome; protein degradation; immune escape; T cells; vaccine immunogen design

HIV traffic and antigen processing pathways in cell subsets

The antigen processing machinery serves many purposes critical to cell maintenance, degrading retiree and misfolded proteins, recycling amino acids for protein synthesis and producing peptides for MHC-I and MHC-II display and immune monitoring (1). Each subcellular compartment contains several proteases and peptidases involved in protein degradation. Cytosolic constitutive proteasomes and immunoproteasomes can unfold and degrade proteins into fragments further processed into peptides by cytosolic aminopeptidases and endopeptidases, some of which are transferred into the ER for further trimming by ER-resident aminopeptidases, ERAP1 and ERAP2, and loading onto MHC-I (2). Exogenous antigens such as proteins, free or antibody-coated viruses, cell debris endocytosed or phagocytosed may be degraded by cathepsins in endosomes and lysosomes. Degradation peptides transferred in the cytosol and endoplasmic reticulum (ER) for further degradation are cross-presented in the vesicular pathway by MHC-I or, in professional antigen presenting cells, transported into the MIIC compartment for MHC-II loading and presentation (1, 3, 4). MHC-II complexes also present endogenous antigens during autophagy, when cytosolic and nuclear antigens are engulfed in autophagosomes fusing with lysosomes for degradation and MHC-II presentation. Autophagy during HIV infection leads

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to HIV MHC-II presentation by dendritic cells (DC) (5). Proteasomes, tripeptidyl peptidase II (TPPII), thimet oligopeptidase (TOP), nardilysin and ERAP1, cathepsins are involved in the processing of some HIV epitopes but few HIV epitopes have been studied with respect to peptidase requirements for production or degradation (6–10). Direct and cross-presentation pathways intersect in many points, as evidenced by the generation of MHC-II-restricted cancer antigen-derived epitopes requiring proteasome processing (11). The role of intracellular antigen traffic in the definition of the MHC peptidome and kinetics of presentation of peptides to immune cells is still poorly understood despite its critical role for immune recognition.

HIV infects cell subsets expressing CD4 and co-receptors CCR5 or CXCR4: CD4 T cells, monocytes, macrophages and dendritic cells (12, 13). Productive infection requires that HIV fuses at the plasma membrane delivering the viral core into the cytosol, proceeds to uncoating and reverse transcription during its transport to the nucleus, and eventually the DNA provirus integrates into the cell genome. The provirus is eventually transcribed and translated into new proteins assembling into immature virions budding at the plasma membrane. Conversely, HIV provirus can enter quiescence and become part of reservoirs persisting despite antiretroviral treatments (14, 15). Productive infection is a rare event since many HIV entry events lead to abortive infection due to the antiviral activity of host restriction factors and of the degradation machinery (16–19). Free HIV virions or antibody-coated particles may be endocytosed or phagocytosed and degraded into endolysosomes or phagosomes. Particles entering in the cytosol can also be subjected to degradation by proteasomes during uncoating (20). After provirus expression, neosynthesized proteins may be degraded and lead to MHC-I presentation (21, 22), while autophagy in HIV-infected cells may lead to MHC-II presentation (23). However, the exact peptides processed and presented by cells have not been extensively defined, rather mostly inferred based on T cell responses in HIV-infected persons. Virus traffic influences both the outcome of viral replication and its degradation, but we still do not comprehend how it contributes to defining the HIV MHC-peptidome and the immunogenicity of HIV proteins. HIV proteins are variably immunogenic within an individual and at the population level (24). HIV Gag p24, Env, Nef are the most immunogenic while Tat or Vpu are poorly immunogenic. The density of putative MHC-I peptide anchors in HIV proteome and the conservation of the proteins across variants or strains do not fully account for such differences. The analysis of degradation patterns of HIV antigens by purified proteasomes (7, 8, 10, 25, 26), or in the cytosol or endolysosomes of primary cells (9, 27–30) identifies areas of proteins quickly degraded into fragments too short be loaded onto MHC-I, while other areas are degraded slower and generate nested degradation peptides of various lengths. The timing of production of epitopes within a protein, even for overlapping epitopes, is variable and in part determined by motifs flanking epitopes (9). These variable degradation patterns and kinetics of production of epitopes may contribute to the variable density of CD8 immune responses within a HIV protein (8–10), but motifs predicting the production of degradation fragments of various lengths and peptide presentation by MHC-I or MHC-II remain to be identified. Aside from degradation patterns, the intracellular stability of degradation peptides also contribute to defining the amount of peptides available of MHC loading (31). The stability of short HIV peptides is surprisingly variable (few seconds to hour), defined by motifs

associated with stability or instability. Algorithms like NetChOP predicting proteasomal cleavage sites (32, 33), sometime in combination with algorithms for TAP or MHC binding (34, 35), help identify some degradation features. But they do not account for other peptidases involved in protein degradation (2), the specificity of the degradation machinery in each cell subset or cellular compartments (7, 27, 28, 36), and viral diversity. Comparison of HIV antigen degradation patterns in cytosol, endosomes and lysosomes identified expected variations in degradation patterns across compartments and showed that some epitopes were produced in all compartments while others were exclusively produced in the cytosol or in the endolysosomal compartment (8, 27–30). These data suggest that the traffic path followed by HIV after entry will shape not only the outcome of infection, but also the timing and nature of degradation peptides available for MHC presentation. Aside from differences during intracellular traffic, the different cell subsets targeted by the virus display variable levels of peptidases activities. As expected from studies in mice (37), macrophages present the highest levels of hydrolytic activities in endolysosomes in accordance with their clearance functions (27, 28). Dendritic cells present higher lysosomal activities than CD4 T cells but low cytosolic peptidase activities (27, 28, 36, 38). Differences in peptidase activities affected the degradation patterns of HIV antigens, the kinetics and amount of epitopes produced. While the surface peptidome of HIV-infected cell subsets has not yet been compared for matched CD4 T cells, DC, and macrophages, it is possible that differences in epitope production will affect the MHC-peptidome, and perhaps the efficiency of immune recognition of various cell subsets by epitope-specific CD8 T cells. Differences in antigen processing activities among cell subsets may be due to variable levels of expression of peptidases, and distinct and unknown mechanisms regulating peptidase hydrolytic activities across cell subsets. The variable effects of proteasome or cathepsin inhibitors on the processing and presentation of HIV peptides between matching monocyte-derived DC and macrophages suggest that various sets of peptidases are involved in the processing and/or degradation of epitopes in each cell type (27). Cell-type specific peptidases, as illustrated for a serine protease unique to monocytic cell line (39), and their contribution to antigen processing and degradation are still poorly defined. The hydrolytic activities of the degradation machinery is finely tuned by external stimuli such as interferon gamma which increases the expression of certain interferon-induced peptidases such as ERAP1 or LAP, the expression of immunoproteasome catalytic subunits, TAP or MHC-I, altogether favoring the processing and display of MHC-peptides (40–42). Various stimuli relevant to HIV infection or vaccination modulate antigen processing. CD4 T cells activated with TCR-dependent or -independent stimuli present higher peptidase hydrolytic activities than resting CD4 T cells. Dendritic cells stimulated with LPS or TLR ligands 7 or 8 (such as CL097 or R848 used as adjuvants in vaccine preparation) decreased cathepsin activities while they increased all peptidases activities in macrophages. These TLR-induced alterations of peptidase activities modulated HIV antigen degradation patterns to various extents (27, 28). Differences in antigen degradation patterns between CD4 T cells and macrophages sustaining productive HIV infection, and DC presenting or cross-presenting HIV antigens during infection or vaccination may affect the pool of peptides available for display by MHC. Additional studies are needed to identify peptides commonly or differently processed in each cell subset, and specifically to assess whether peptides commonly

processed in all cell subsets may constitute better targets for immune clearance of infected cells.

Sources of antigens and the MHC-peptidome in HIV infection

Owing to the technical difficulties to isolate MHC-peptides from large numbers of HIV-infected cells, limited datasets exist on the HIV-derived immunopeptidome, and all were published in the past 3 years (43–46). While the three groups used various experimental systems (cell line expressing soluble MHC, primary CD4 T cells infected with replicative HIV, B cells infected with non-replicative HIV, 293T cells transfected with HIV, cells infected with a MVA vector expression HIV antigen fragments), they all showed that HIV-derived MHC-peptides come mostly from the structural and most abundant Gag proteins, but also from other less abundant proteins. Some areas of the Gag proteins seem efficiently presented across different cell types, HIV expression systems or HLA types. Mechanisms underlying differences in presentation of HIV peptides within Gag or across HIV proteins are still not understood despite their critical roles to identify targets for immune recognition and immunogen design. They may include variable degradation patterns of HIV proteins in various cell subsets and subcellular compartments as well as presence or absence of anchors for TAP and MHC binding.

HIV peptides presented by MHC-I included peptides of 8–11aa of optimal size for MHC-I loading, and peptides of non-canonical sizes of up to 16aa (43–45). The presentation of longer peptides is in agreement with findings on self-derived and cancer-associated peptides (47–50). The presentation of some longer peptides with extensions on the N- and/or C-terminal side was not predictable based on potential anchors for MHC-I binding. These findings raise questions about the location and loading of such peptides onto MHC, the structure of the MHC-peptide complexes and stability of the MHC-peptide at the cell surface for potential CD8 recognition. However, the unbiased identification of MHC-bound peptides led to the identification of additional responses in HIV-infected persons and will be important to define targets for immune recognition of infected cells or peptides displayed by DC after vaccination. Strategies to clear HIV reservoirs aim at reactivating latently infected cells with various latency reversal agents (LRAs) and antiretroviral therapy, leading to HIV re-expression and peptide presentation for immune clearance (14, 51, 52). Pre-existing HIV immune responses elicited during HIV infection may not efficiently clear LRA-reactivated reservoirs (53–55). Thus, it will be important to identify HIV peptides displayed by latently infected cells after provirus reactivation with LRAs and assess whether new HIV-specific responses need to be induced in the context of therapeutic vaccination.

The antigenic sources of MHC-peptides derived from HIV may vary during viral replication but have not yet been precisely identified. Incoming virions provide functional HIV proteins for degradation in the cytosol, in endolysosomes or phagosomes leading to MHC presentation and T cell immune recognition (27, 56, 57). During provirus translation, in addition to complete proteins, defective ribosomal products (DRiPs) (58–60) may contribute to HIV peptide presentation (21, 61, 62). They could contribute to providing peptides for early MHC presentation and artificially directing HIV Gag to the DRiP pathway with a N-end rule degradation signal increased MHC-I presentation of HIV (62). Alternate reading

frame translation products of HIV such as ASP (63) have been identified in HIV-infected cells and their role in HIV replication is unknown. While these products are difficult to isolate from cells, the existence of translation products derived from alternate reading frames is indirectly demonstrated through the identification of MHC-I restricted immune responses in HIV-infected persons (64, 65), and from HLA-restricted mutations within these reading frames (66–68). Recent studies on the self MHC-peptidome revealed novel categories of unexpected sources of MHC-peptide not coming from mistakes in protein translation (69) but from abnormalities during protein degradation or peptide loading onto MHC-I (70, 71). Spliced peptides made of two non-contiguous degradation fragments re-ligated in the proteasome during degradation were first identified in a few cancer antigens and shown to be immunogenic in patients (72–77). A recent study combining mass spectrometry and complex bioinformatics analysis (78) showed that spliced peptides account for up to 30% of the MHC-self-derived peptidome (70). CD8 T cell immune responses against spliced peptides derived from Listeria were also identified in Listeria-infected mice (79), suggesting that peptide splicing can occur during pathogen infection in vivo. A novel category of hybrid MHC-peptide was recently identified: the dual peptide occupancy of MHC-I by two short non-contiguous and separated short peptides of 2–7aa (71). Such peptides derived from two EBV antigens generated CD8 T cell responses, suggesting that mix-and-match of short peptides occupying MHC-I groove may contribute to the MHC-peptidome (71). It still remains to be investigated whether spliced peptides or mix-and-match peptides can be generated in HIV-infected cells, but the existence of potential new categories of unconventional peptides displayed by infected cells may help define novel HIV-specific immune responses relevant to vaccine design.

HIV adaptation to the antigen processing machinery and immune escape

HIV-specific CD8 and CD4 immune responses have been extensively identified in thousands of HIV-infected persons and defined in term of peptide specificity, HLA restriction, frequency of immune responses at the population level, TCR clonotypes, cytokine production, proliferative or killing capacities, yet the correlates of immune protection are still not well defined (80–84). HIV-specific T cells play a significant role in controlling viral load during acute infection and during spontaneous control in HIV controllers (81, 85–87). The temporal association between the reduction of viral load in acute infection and the appearance of T cell responses (88–90), and the HLA-restricted immune pressure driving HIV evolution (91–95) provide indirect evidence of the role of T cell in controlling viral load. However, these T cells do not clear infection. Factors contributing to their lack of efficacy include non-protective immunodominant responses (96), immune pressure exerted by T cell responses driving mutations in the virus and immune escape (92, 97, 98), long-term antigen stimulation leading to T cell exhaustion (99), and rapid establishment of viral reservoirs invisible to immune cells (51, 100).

Specific HLA such HLA-B57 or -B27 and CD8 or CD4 T cell responses against Gag polyprotein (101–105), superior multifunctional T cell responses (81, 86, 106) and subdominant rather immunodominant immune responses (96, 107, 108) are associated with lower viral load and spontaneous control, but the mechanisms underlying these associations to viral control are not fully understood (109). The search for correlates of immune

protection has focused on the functionality and specificity of the CD4, CD8 T or NK cell responses elicited during infection but little is known on the contribution of antigen processing and presentation to the antiviral capacity or immunodominance of these immune responses. As T cell responses are activated through MHC-peptide recognition, fundamental outstanding questions are the nature and relative amount of HIV peptides displayed by HIV-infected cells across multiple HLAs, and how efficiently HIV-specific T cells primed during infection detect HIV peptides naturally processed and presented by infected cell subsets. No comparative datasets exist on MHC-peptide displayed by CD4 T cells, macrophages and DC of the same donor after HIV infection. Differences in antigen processing activities and degradation patterns of HIV proteins between CD4 T cells and other cell subsets (7, 27–29) point toward potential variations in peptide presentation. If so, the most efficient immune responses should be defined as those targeting commonly presented peptides, in addition to the already described multifunctional capacity of HIV-specific immune cells.

It will be important to identify factors driving HIV immunodominance during infection to avoid reproducing such hierarchy during vaccination. Immunodominance in viral infection is multifactorial and, depending on the epitopes, may be attributed to differences in antigen processing, TAP, MHC or TCR binding affinity (110, 111). Similarly HIV T cell hierarchy may be shaped by the degradation patterns of antigens (9, 10), kinetics of epitope production in cell extracts or in DC endolysosomes (27, 31), as well as MHC and TCR binding affinity (112–114). Errors during retro-transcription of HIV RNA into DNA combined with HLA-restricted immune pressure lead to a diversification of HIV within a person and across the population (91, 92, 115). Some HLA-restricted mutations reduce viral replication capacity (116–118). The impact of HLA-restricted mutations are some mitigated by additional compensatory mutations re-establishing sufficient viral fitness for propagation (119, 120), as only limited evolution is tolerated in structurally constraint sites of HIV proteins (118, 121). Mutations preventing proper peptide recognition by T cells render many immunodominant early responses irrelevant and lead to the broadening of immune responses in the chronic phase of infection (122–124). HIV has developed many mechanisms to avoid or limit its presentation to immune cells, including the down-modulation of MHC-I (125–127), and a remarkable adaptation to the antigen processing machinery. Many HLA-restricted intraepitopic mutations at anchor sites for MHC binding (113) or at residues required for contact to the TCR prevent T cell recognition while degeneracy is tolerated within epitopes at sites not critical for MHC or TCR binding (128). More recent studies have focused on identifying patterns defining antigen processing mutations during viral evolution. A study defining residues cleavable or non-cleavable by aminopeptidases showed that mutations toward to a poorly cleavable residue reduce epitope production (129). At the population level, residues flanking an HIV epitope tend to mutate under pressure of the restricting HLA toward poorly cleavable residues and are therefore predicable (129). HLA-restricted mutations within epitopes observed frequently in people sharing one HLA tend to reduce intracellular peptide stability, the amount of peptides available for CTL recognition and immune escape (31). As intracellular peptide stability or instability is determined by specific motifs, this pattern of immune escape could be predicted in a population (31). Studies on antigen degradation patterns of HIV variants showed that HIV of various clades adapt to the most frequent HLAs leading to immune evasion at the population level (26, 115, 129, 130).

A better understanding of antigen degradation and development of computational tools incorporating both diversity of the degradation machinery and sequence diversity of HIV will permit us to fully identify signatures of immune escape at the population level, and conversely to define motifs associated with efficient peptide presentation.

Exploiting the knowledge on HIV antigen processing to improve vaccine design

The ultimate purpose of HIV research is to create vaccines to prevent infection (prophylactic vaccine) or to enhance immune functions and clear viral reservoirs in HIV-infected persons to the point where they may not need antiretroviral treatments (therapeutic vaccines) (51, 131, 132). Vaccine trials in humans have not been successful so far at achieving these goals, but it is likely that a successful vaccine strategy will encompass both antibody responses to block viral entry and T cell responses to prevent cell-to-cell transmission or clear reservoirs (131, 133). Multiple animal studies exploring various types of immunogens or viral vectors are showing encouraging results (134–138).

The high diversity and rapid evolution of HIV sequences within a person or across the population, the existence of different clades on different continents and the diversity of HLA combinations in the human population is a major challenge for the design of a universal HIV immunogen (115, 132, 139). Vaccine strategies should avoid reproducing the narrow immunodominance of immune responses elicited during infection and increase adequacy or breadth of immune responses. Two opposite approaches are being explored to design immunogens. The first design retains only the most conserved areas of HIV proteins in the immunogen plus the most frequent variant allowing coverage of the vast majority of conserved HIV areas across clades (140–142). The definition of conserved areas in HIV may include both conservation of the protein sequence, co-evolving areas in which mutations dramatically reducing viral fitness loss and compensatory mutations are detected consecutively (140, 142–145). Immunogens based on conserved elements encoded by a MVA-based viral vector yielded CD4, CD8 and antibody responses in mice and monkeys and clinical trials are underway to test their safety and efficacy (107, 143, 144, 146–148). Alternatively, mosaic immunogen design (139, 149) aims at including sequence variability of 9-mer epitopes by computationally assembling variants in mosaic constructs. Such immunogens encoded by adenovirus-based vectors elicited T cell and antibody responses and promising results in Macaque vaccination experiments (135) and are tested in clinical trials.

Perhaps the most intriguing and promising results in Macaque models came from a novel vaccine approach using an attenuated Rhesus CMV vector with limited cellular tropism (134, 150). While all Macaques vaccinated with the RhCMV expressing several complete SIV proteins developed SIV infection, 55% of them cleared SIV infection for at least 3 years post-challenge. All vaccinated Monkeys elicited broad and sustainable CD4 and CD8 T cell immune responses covering >65% of the SIV antigens used in vaccination (151, 152). Surprisingly CD8 T cell immune responses were restricted by MHC-II (153) and MHC-E (154). Mechanisms underlying the priming of unconventional and broad immune responses

and breaking the immunodominance observed during infection of vaccination with MVA- or adenoviral vectors expressing full proteins are still unknown. They may be related to the limited tropism of the attenuated RhCMV vector and specific cell subsets infected by the viral vectors in lymph nodes, the persistence of the antigen or any effect the vector may have on antigen processing and presentation. Whether a human CMV vector attenuated enough to be safe in the human population will trigger similar immunogenicity and clearance of HIV infection is still unknown.

These promising studies also highlight our incapacity to predict the outcome of vaccination in term of types and breadth of immune responses elicited by the vaccine and of its protectiveness after infection in the human population. They also provide guidelines for the definition of new correlates of immune protection and parameters to assess during vaccine design strategies. Immune responses elicited by the vaccine should be evaluated not only for their breadth and polyfunctionality but also to allow recognition of peptides naturally processed and presented by HIV-infected cells. It would therefore be important to assess whether vaccines processed and presented by dendritic cells lead to presentation of peptides similar or overlapping those presented by HIV-infected cells subsets. Considering the effect of viral infection (155) on the antigen processing machinery, it will be interesting to determine how viral vectors selected for HIV vaccines (MVA, adenoviruses, potential attenuated hCMV vector or other attenuated vectors derived from Lysteria or HSV (156–158) and adjuvants (28, 159, 160) will affect immunogen processing and presentation. It will be essential to understand how peptide presentation by DC correlates with the breadth of immune responses, and to determine if and how peptide presentation by DC may be used to predict immunogenicity before proceeding to expensive animal studies. The use of flanking motifs to modulate and optimize peptide presentation (for instance linkers inserted between conserved areas of HIV proteins for conversed elements immunogen design) may provide an additional way to improve peptide presentation by DC (9, 161–163). The identification of MHC-E-restricted immune responses elicited by the RhCMV vector renewed interest in the HLA-E-restricted peptidome beyond the well-known presentation of MHC-derived sequence signal in immune tolerance (164–166). One HIV peptide predicted to be presented by HLA-E (167) triggered cytolytic NK cell responses (168), supporting the role of HLA-E peptide presentation for immune clearance. A complete mapping of the HLA-E peptidome displayed by HIV-infected cells is necessary and may identify novel relevant targets for immune clearance. How to specifically induce HLA-E-restricted HIV immune responses during vaccination remains to be determined.

The expanding understanding of HIV antigen processing mechanisms and the unbiased identification of the HIV-derived immunopeptidome, together with better computational tools to predict antigen processing and presentation in the context of antigen variability, will help define the most relevant targets for immune recognition and help improve vaccine design. Knowledge, assays and bioinformatics tools developed to tackle these HIV-focused questions will also be relevant to the design of vaccines against other chronic infections or cancer.

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Highlights

- HIV antigen processing varies across cell subsets relevant to HIV infection or vaccination.
- HIV has adapted to the antigen processing machinery at the population to limit its presentation to immune cells.
- Sequence signatures of immune escape or of degradation patterns are being identified and may help predict peptides presentable by various MHC complexes.
- Recent studies on MHC---peptidome of HIV---infected cells identify peptides of unconventional lengths and novel targets for immune recognition.
- In---depth analyses of HIV---derived antigens and MHC---peptidome and better computational tools to predict antigen processing in the context of HIV variability will help design vaccine immunogens eliciting immune responses leading to early and efficient recognition of infected cells.