



Molecular mimicry of HIV gp120: Possible implications on prevention and therapy of AIDS

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ABSTRACT

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A broad range of similarities between HIV-1 gp120 and human proteins—especially those participating in immune responses—highlight gp120 as a pleiotropic protein which can influence many important functions of the human immune system. The molecular mimicry that serves to the human immunodeficiency virus as potent destructive arms against immune system could be the weak point we are in search of over decades. Examples involving sequence and informational similarities of HIV-1 gp120 and immune-related host cell proteins important for prevention and treatment of HIV infection are presented.

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INTRODUCTION

For more than three decades, molecular mimicry has been considered as an important, contributing factor in the pathogenesis of viral infections. Virus-bearing molecular structures similar to those expressed on the surface of normal cells, could elicit the immune response against the host proteins. Alternatively, the immune system can recognize these viral determinants as "self" antigens, which allows the virus to escape the immune system surveillance. In the context of AIDS pathogenesis, some have argued over the years that the phenomenon of the molecular mimicry could represent a significant factor in the HIV disease expression (1-6). This particularly concerns the HIV-1 envelope glycoprotein gp120. A broad range of structural, functional, and immunological similarities between HIV-1 gp120 and human proteins, especially those participating in immune responses, highlight this viral component as a pleiotropic protein that can in different ways affect many important functions of the human immune system contributing in that way to development and progression of HIV disease. The molecular mimicry of HIV-1 gp120 also represents the main obstacle in the development of an effective and safe AIDS vaccine (7,8). Thus, it is of considerable interest to investigate the molecular mimicry between HIV-1 gp120 and human proteins and the possible impacts of this phenomenon on prevention and therapy of AIDS.

HIV ENVELOPE PROTEIN AND IMMUNE-RELATED HOST MOLECULES

The general picture of HIV mimicry is particular rather than uniformly generic. The major fraction of the reported HIV mimicry involves immune-related host proteins—HLA, Ig, complement, etc. and any connection to immunopathology is suggestive. The following table (Table 1) of mimicry claims in the literature involving gp120 and immune-related host cell protein sequences attempts to present the most prominent examples.

Infection by human immunodeficiency virus type 1 (HIV-1) leads to progressive destruction of the CD4+ T-cell subset, resulting in immune deficiency and AIDS. The specific binding

of the viral external envelope glycoprotein of HIV-1, gp120, to the CD4 molecules initiates viral entry. An essential coreceptor for HIV either CCR5 or CXCR4, both of the chemokine-receptor family, cooperates sequentially with CD4 to facilitate HIV entry into target cells. In spite of considerable divergence among different HIV-1 isolates, gp120 molecules preserved their binding tropism for the CD4 receptor, as well as its major coreceptors. That is why a considerable interest is paid to examination of conserved regions of gp120 molecule.

Table 1. Mimicry claims in the literature involving HIV envelope protein gp120 and host-cell protein sequences

Source	Protein Coordinate	Ref.
IgG1, IgG2, IgG3	88-97	9
HIV-1/gp120(DJ258A)	55-65	
HLA DR II beta 142-151	142-151	10-12
Fas antigen	275-280	
HIV-1/gp120 (IBNG)	251-260	
HLA DR alpha	28-40	10
HIV-1/gp120 (2HT596.4)	270-282	
HLA class I C alleles	66-69, 79-82	13
HIV-1/gp120 (HXB2R)	485-487,500-503	
CD4 receptor	60-64	12,14,15
HIV-1/gp120 (IBNG)	108-112	
TCR alpha-chain	26-46	12,15
HIV-1/gp120	212-232	
Ig light chain V region	37-48	16
HIV-1/gp120 (NL43)	308-328	
Ig light chain V region	29-39	16
HIV-1/gp120 (HXB2R)	453-463	
Ig light chain	450-460	17
HIV-1/gp120 (LAI)		
SDF-1beta	32-93	18
HIV-1/gp120 (HXB2)	296-353	

The C-terminus of second conserved region of HIV-1 gp120 and the first framework region (FR1) of the human IgG heavy chain variable region (subgroup III), VH III contain a similar motif VQL(N)VES in their sequences (19,20). The nucleotide sequence GCTGGTGG,

encoding the amino acids QLV of this motif, represents the Chi signal promoting generalized recombination in prokaryotes (21,22). Downstream from the putative Chi sequence, a heptamer sequence, CAGTCTG, has been identified (20). Five of the seven bases in this nucleotide sequence match the consensus recombination signal CACTGTG already found to be involved in V-(D)-J recombination of the Ig gene (23). It is of note that a similar sequence exists at the same position in the gp120 gene of nearly all HIV-1 isolates.

Within the VH III gene, 260 nucleotides downstream from the Chi sequence the second IgH-specific recombination signal, TACTGTG, have been located (22). The HIV-1 gp120 gene, downstream of the Chi-like sequence at a similar distance (260-270 nucleotides, depending on the viral isolate), contains the homologous sequence TACTGTA, representing the putative recombination signal. This nucleotide sequence is also conserved in all HIV-1 isolates. Both of the above recombination signals, whose positions are given in Figure 1, have been shown to take part in rearrangement processes in heterogenous systems.

In the frame of experimental study which succeeded (25) the complete and active Chi recombination spot has been identified in sera of AIDS patients using a chimeric primer consisting of the nucleotide sequence derived from the HIV-1 envelope gene coding for the second conserved region of gp120 and the highly conserved sequence derived from the human immunoglobulin gene coding for the VH III domain. We have demonstrated *in vivo* the recombination between the HIV-1 env gene and the bacterial gene coding for the clp protease. This RT-PCR study which included 11 HIV-positive individuals. Sera were analyzed using the PCR primers P1 (TTGGAGAGCAATGGCTAGTGA) and P3 (ATTTCGGGGTCCC-CTCCTGA), which are derived from the 55 strongly conserved regions of the pol and env genes and which are highly specific for HIV-1 (24), as well as the chimeric primer P2 (ATAGTACAGCTGGTGGACTCT) containing the nucleotide sequences ATAGTA and CTCT derived from the gp120 gene domain coding for the second conserved domain (C2) and the consensus sequence CAGCTGGTGGGA derived from the human VHIII gene domain coding for the FR1 region. In the first step of this analysis, a large fragment of the HIV genome was amplified from all 11 HIV-positive sera by RT PCR using the primer pair P1=P3. The subsequent nested RT-PCR using the primer pair P2=P3 showed in 3 out of 11 analyzed HIV positive sera, bands corresponding to sequences of about 260-270 nucleotides long (lines 1, 2, and 3 in Figure 1a). These RT-PCR - amplified fragments correspond to the expected site of the HIV-1 gp120 gene encoding the C-terminus of the C2 region, the entire V3 loop, and a large portion of the C3 region. An example of RT-PCR amplification of an HIV-positive sera that does not contain the HIV subclone carrying the Chi sequence within the gp120 gene is presented in line 5, Figure 1a. Three control sera collected from HIV negative blood donors under the same experimental conditions showed no PCR amplification. An RTPCR corresponding to one of these three negative controls is given in Figure 1a (line 4).

The fragment obtained from one of three Chi-positive samples containing the highest amount of the amplification product (the first line in Figure 1a), was cloned into a plasmid vector, and the obtained clone was sequenced (Figure 1b). Scanning of the HIV database (24.) showed that the nucleotide sequence within primers P2 and P3 does not belong to HIV. Further analysis performed by examination of the EMBL nucleotide database (26) by the BLASTX program revealed that the main part of this sequence represents, with high probability, a part of the gene encoding the clp protease. The highest homology score (S) and the lowest value of the expected frequency of chance occurrence (E) indicate that this evolutionarily highly conserved gene with highest probability belongs to *Haemophilus influenzae* (Figure 1c). The closest values of the parameters S and E in this analysis are obtained for the clp gene from *E. coli*. It is important to note that both of those bacterial systems utilize the Chi recombinational stimulator (27).

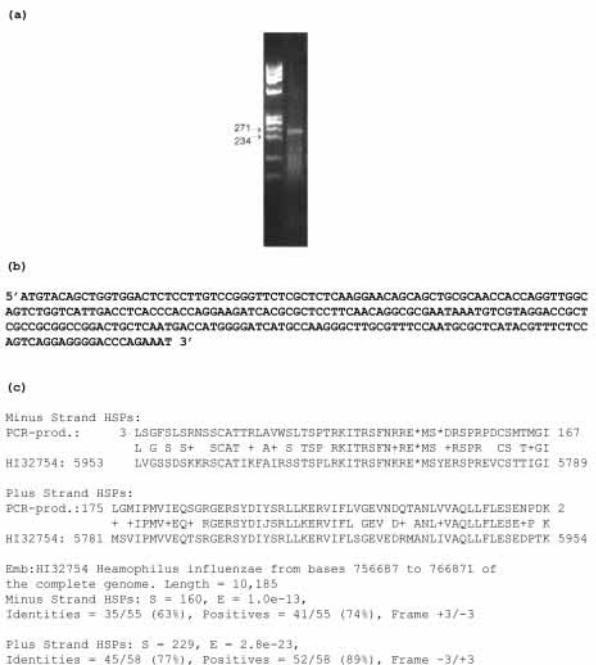


Figure 1. Results of the RT-PCR study of HIV-positive and HIV-negative sera. (a) RTPCR using the primer pair P2=P3 on total RNA from three HIV-positive sera containing HIV subclones carrying Chi recombinational stimulator (lines 1, 2, and 3), the HIV-negative serum (line 4), and the HIV-positive serum, which does not contain the HIV subclone carrying the Chi sequence (line 5). At the far left is molecular size marker. (b) The nucleotide sequence obtained by cloning and sequencing of the PCR product presented in line 1 (primers are underlined); (c) homology of the gene product corresponding to the nucleotide sequence derived from the PCR product (Figure 1b) and the clp protease from the *H. influenzae*. Note: Statistical significance is estimated under the assumption of the equivalent of one entire reading frame of the query sequence and one entire reading frame of the database code for protein, and that significant alignments will only involve coding reading frames.

As a consequence, the gp120 antigen employed as vaccine component could, through its immunoglobulin features, influence the host immune system. Beside that, candidate AIDS vaccines based on recombinant viruses, including vaccinia virus, Polio virus, influenza virus, Hepatitis B virus, canarypox virus, etc., that carry the HIV-1 gp120 gene are currently under consideration (28). Described properties of the HIV-1 gp120 gene indicate that, viral vectors carrying it could represent potential new pathogens with unpredictable effects on the immune system.

HIV ENVELOPE PROTEIN AND THE IMMUNOMODULATOR VASOACTIVE INTESTINAL PEPTIDE

It has been generally assumed that host factors play an important role in determining the clinical outcome in HIV infection, since HIV disease progression varies greatly in different individuals. In order to define these host factors, Neurath and coworkers have investigated antibody profiles in two groups of HIV patients: those who remained healthy for at least 10 years and those who developed AIDS within 5 years of the onset of infection (29). It was demonstrated that antibodies recognizing the peptide RSANFTDNAKTIIVQLNESVEINCTRP (amino acids 280-306 of the envelope protein gp120 from the BH-10 isolate of HIV-1) are significantly more prevalent in asymptomatic carriers than in AIDS patients. Based on these results, it was concluded that absence or disappearance of detectable antibodies reacting with the gp120-specific epitope mimicked by synthetic peptide 280-306 might represent a possible factor contributing to the development of AIDS. For this reason it has been proposed that the maintenance of a high level of these antibodies by immunotherapy based on active immunization with antigens containing this peptide, and/or administration of the corresponding antibodies, should be considered as a modality for therapy of HIV-1 infection.

Despite the presence of the strongest T cell epitope of gp120, which is active in vitro (30), and an exposed B cell epitope (31,32), the C-terminus of the second conserved region (C2) of HIV-1 gp120-encompassing amino acids 280-306 is not immunogenic in humans (30,33,34). One possible conclusion drawn from these findings might be that the human immune system is unresponsive or tolerant to this epitope. It has been postulated that immunological tolerance to this HIV-1 gp120 domain might be the consequence of similarity between the region comprising the T cell epitope and its immediate vicinity, and some proteins participating in the human immune response. This assumption was confirmed by the local similarity between the C-terminus of the second conserved region of HIV-1 gp120 and several human proteins, presented in Figure 2 (19,35).



Figure 2. Sequence homologies between the C-terminus of the second conserved region of HIV-1 gp120 and human proteins. The asterisk (*) indicates residues that are identical, and the sign (+) indicates a conservative change (6).

Absence of the active T cell epitope within this peptide raises the question of the origin of antibodies in human sera reacting with Neurath's peptide. It has been postulated that these antibodies represent autoreactive antibodies elicited by some human antigen (36).

In order to identify candidates for this autoantigen, human sequences from Swiss-Prot protein database were analyzed using the Informational Spectrum Method. This method is used for the analyses of protein sequences by signal processing techniques. According to this approach, protein sequences are transformed into signals by assignment of numerical values to each amino acid. These values correspond to the electron-ion interaction potential (41), determining electronic properties of amino acids responsible for their intermolecular interactions (42). The signal obtained is then decomposed in periodical functions by Fourier transformation. The result is a series of frequencies and their amplitudes. The obtained frequencies correspond to the distribution of structural motifs with defined physico-chemical characteristics responsible for the biological function of the protein.

The informational spectrum calculated for the peptide 280-306 is presented in Figure 3a. As can be seen, it contains only one characteristic pick corresponding to the frequency F(0.218). The computer assisted search of the Swiss-Prot database revealed the vasoactive intestinal peptide (VIP) as the only protein among analyzed human proteins that possesses such a spectral property (Figure 3b). Furthermore, the domain of the peptide 280-306 with an informational spectrum most similar to VIP has been identified (Figure 3c). This region corresponds to the sequence RSANFTDNACTIIVQLNESVEIN (denoted as the peptide NTM) (36). It is of note that the second dominant common frequency component F(0.031) in the informational spectra of VIP and the peptide NTM was previously identified as spectral characteristic representing information that is responsible for interaction between HIV

and the CD4 receptor (43). In Figure 3d is the sequence homology between peptides VIP and NTM. These results point at VIP as self-antigen eliciting autoantibodies that react with peptide identified by Neurath and co-workers, and this possibility was experimentally tested (37). Presence of the anti-VIP antibodies have been reported in high concentration in sera from asthma patients (38) and in lower concentration in sera from normal healthy individuals (39,40). Affinity chromatography on agarose-bound VIP peptide to compare antibody binding to NTM and VIP was used. The elution profiles represented by Veljkovic et al. (44) are in fact nearly identical, suggesting that both peptides may bind to the same fraction of antibodies. The above-presented results clearly demonstrate functional and immunological crossreactivity between HIV-1 gp120 and VIP.

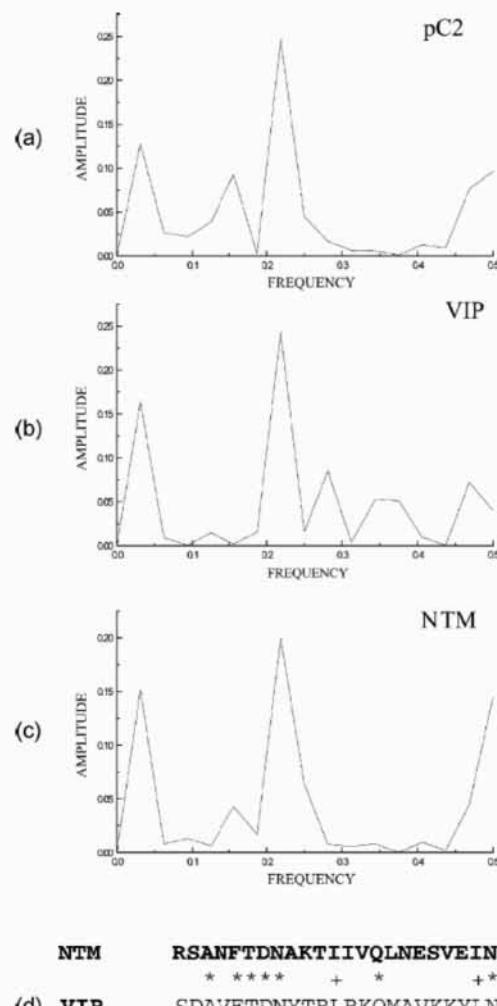


Figure 3. Spectral and sequence similarities between the peptide 280-306 derived from HIV-1 gp120, the peptide NTM, and VIP. (a) The informational spectrum (IS) of the peptide 280-306, (b) IS of VIP, (c) IS of the peptide NTM, and (d) sequence homology between the peptide NTM and VIP. For each spectrum, the abscissa represents the frequencies from the Fourier transform of the sequence of the electron-ion interaction potential corresponding to the amino acid sequence. The lowest frequency is 0.0 and the highest is 0.5. The ordinate represents amplitudes, in arbitrary units, corresponding to each frequency component of the spectrum. (d) The * indicates residues that are identical, and the plus sign indicates a conserved change.

As a corollary, correlation between the titer of VIP=NTM-reactive antibodies and the HIV-disease progression indicates that these antibodies may be an important factor in control of the disease. Based on this, the possibility of applying passive immunization, based on the VIP=NTM-reactive antibodies, as a therapy for HIV disease was taken in consideration (22).

CONCLUDING REMARKS

The presented examples shows that the molecular mimicry that serves to the human immunodeficiency virus as a powerful destructive arms against immune system of the host could be the weak point we are looking for over decades. Immediately after the discovery of the human immunodeficiency virus (HIV), development of AIDS vaccine became a challenge for scientists worldwide.

During the past 20 years, the pendulum of opinion in the HIV-1 vaccine field has swung between two extremes, initially favoring the induction of antibodies only, and subsequently favoring the induction of cell-mediated immune responses only. At present, the consensus seems to be that induction of both humoral and cellular immunity by an HIV-1 vaccine will be required to achieve maximum protection. One obstacle to the development of an effective HIV-1 vaccine has been the difficulty in inducing broadly reactive, potent antibodies with protective functions. Defining epitopes and designing immunogens that will induce these antibodies is one of the main challenges that currently confront the HIV-1 vaccine field.

A broad range of structural, functional, and immunological similarities between HIV-1 gp120 and human proteins—especially those participating in immune responses—highlight gp120 as a pleiotropic protein which can, in different ways, affect many important functions of the human immune system.

This situation opens the fundamental question: is a safe and effective, preventive AIDS vaccine possible at all, or is its current lack only the consequence of our incomplete knowledge?

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