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Interaction between human interleukin-16 and CD4 receptor of HIV-1[1]

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KEY WORDS molecular structure; interleukin-16; CD4 antigens; computer-aided design; protein conformation

ABSTRACT

AIM: To study the interaction between human interleukin-16 (IL-16) and the receptor CD4 (T-lymphocyte differentiation antigen) of human immunodeficiency virus type 1 (HIV-1). **METHODS**: Two structurally conserved regions (SCRs) of human IL-16 were built by the SYBYL/Biopolymer module using the corresponding transmembrane (TM) domain of human interleukin-4 (HIL-4) and HIL-2 as the templates. The coordinates for amino-terminal residue sequence, carboxyl-terminal residue sequences, and cytoplasm loops were generated using Biopolymer's LOOP SEARCH algorithm. **RESULTS**: HIL-16 first formed a homodimer, then contacted with CD4 dimer further forming a dimeric complex. Subsequently, the dimeric complex constructed the tetrameric complex by two disulfide bridges between the cysteines of HIL-16 (Cys31-Cys31). **CONCLUSION**: The interaction model is useful to propose the action mechanism of HIL-16 and is beneficial for rational designing of novel anti-HIV drugs.

INTRODUCTION

Interleukin-16 was originally described in 1982 as a T-cell specific chemoattractant factor and therefore named lymphocyte chemoattractant factor (LCF)[1]. IL-16 is produced by $CD8^+$ lymphocytes and has been reported to inhibit HIV-1 and SIV replication in infected PBMC[2]. The human immunodeficiency viruses (HIV-1 and HIV-2) and simian immunodeficiency viruses (SIV) are the etiologic agents of acquired immunodeficiency syndrome (AIDS) in their respective human and simian hosts[3]. Virus attachment also involves the interaction of the gp120 envelope glycoproteins with specific receptors such as the CD4 glycoprotein and members of the chemokine receptor family. CCR5 (cell chemokine receptor type 5) and CD4 are coreceptors for immunodeficiency virus to enter target cells. A major function of CD4 binding is to induce conformational changes in the gp120 glycoprotein that contribute to the formation and/or exposure of the binding site for the specific chemokine receptor[4]. Several primary SIV isolated no longer depend on CD4 for efficient entry, and bind to chemokine receptor without prior CD4 interaction[5].

On the other hand, interleukin-16 shares agonistic effects on $CD4^-$ lymphocytes with anti-CD4 antibodies and HIV-1 gp120, while IL-16 and gp120 share a common receptor, CD4 glycoprotein[1]. Unlike HIV-1 gp120, IL-16 suppress cell proliferation without modulating CD4 from the cell surface. The activity of IL-16 is absolutely dependent upon the presence of membrane-expressed functional CD4 based on previous studies[6]. IL-16 has been shown to function as chemoattractant factor, as a modulator of T-cell activation, and as an inhibitor of immunodeficiency virus replication. The naturally secreted bioactive form of IL-16 is produced as a mature 130-amino acid protein with neither a signal peptide nor further processing[7]. CD4 serves as a receptor for the secreted form of IL-16, and IL-16 binding to CD4 induces signal transduction, while affects the activation state of the cell[2]. Moreover, the tetrameric structure of IL-16 appears to be an absolute requirement for IL-16 bioactivity, and fully assembled; bioactive, tetrameric protein is present preformed only in $CD8^+$ T cell. Although the three-dimensional structure is not known, there is some evidence that the 15 hydrophilic, C-terminal amino acids might be important in IL-16 binding to its receptor, CD4[1]. Although IL-16 and HIV-1 gp120 both

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use CD4 as a receptor, antibody and peptide binding studies indicate that they do not share a common binding site. Studies indicate that the IL-16 binding site on CD4 may be in close vicinity to the epitope recognized by the anti-CD4 mAb OKT4 in the V4 domain, whereas HIV-1 gp120 binds to the V1 region of CD4[7]. Thus, it is unlikely that IL-16 sterically inhibits HIV-1 binding to CD4. Moreover, IL-16 represses the HIV-1 promoter. Since the β-chemokines MIP (macrophage-inflammatory protein)-1α, MIP-1β, and RANTES inhibit HIV-1 replication by blocking virus entry, it is clear that IL-16 and the β-chemokines repress HIV-1 at different points in its replication cycle, thus these naturally occurring anti-HIV-1 cytokines should be considered for their combined therapeutic potential.

However, IL-16 may play a role in a tetrameric structure despite its unknown 3D structure. Moreover, IL-16 has been shown to function as chemoattractant factor, as a modulator of T-cell activation, and as an inhibitor of immunodeficiency virus replication. Furthermore, these properties are similar to those of some interleukins, such as IL-15, IL-13, and IL-4. IL-15 can enhance immune functions during HIV infection and may play a significant role in regulating immune mechanism[8]. IL-4 and IL-13 markedly and significantly inhibited HIV replication at the transcription level in monocyte-derived macrophages, and this occurred whether these cytokines were added before or after HIV infection[9]. These interleukins (IL-2, IL-4, IL-13, and IL-15) belong to the short-chain class of four-α-helical bundle cytokines, a family of proteins with a characteristic up-up-down-down four-α-helical topology[10]. Thus, we made a hypothesis that the secondary structure of IL-16 was predicted as a helical cytokine and may belong to the short-chain class of four-α-helical bundle proteins because of its potential biological activities and its sequence length being generally smaller than 150 residues. On the other hand, HIL-5 is a disulfide-linked homodimer with 115 amino-acid residues in each chain. The crystal structure at 2.4 A resolution reveals a novel two-domain structure, with each domain showing a striking similarity to the cytokine fold found in IL-2, IL-4, and GM-CSF[11]. This is helpful for building the dimer of human interleukin-16.

In this report, we generated the structural models for human interleukin-16 and the interactions between HIL-16 and its receptor, CD4.

METHODS

Molecular modeling of 3D structure of HIL-16 was performed on a Silicon Graphics Iris Indigo (SGI Inc, Silicon CA, USA) workstation using the Biopolymer module of the commercial software packages SYBYL V6.3 (Tripos Inc, St Louis MI, USA).

The homology comparison of HIL-16 with HIL-2 and HIL-4 The sequences of human interleukin-16, HIL-2, and HIL-4 were compared by the software packages MSA version 1.0 (Multiple Sequence Alignment, InforMax Inc). The sequences of HIL-16, HIL-2, and HIL-4 come from GeneBank (AC code separately Q14005, P01585 and P05112).

Molecular modeling of HIL-16 Two high-resolution X-ray crystal structures of HIL-4 (PDB code file 2INT) and HIL-2 (PDB code file 3INK) were used as template structures to create independent HIL-16 models (Tab 1). Using the structures of HIL-4 and HIL-2 as templates, each α-helices was superimposed on to the corresponding position in the template structure. Then, the average model of SCRs (structurally conserved regions) was generated. The N-termini, C-termini, and loop segments were generated using Biopolymer's LOOP SEARCH algorithm. Automatic adjustments were made to remove the unfavorable steric interactions and to make the model consistent with the mutational data. The total energy was minimized via molecular mechanics. The primary models were now optimized for 200 steps with the steepest descent minimization and subsequently for 2000 steps with conjugate gradient minimization, using

Tab 1. Sequence alignment of the four helical fragments of IL-2, IL-4, and IL-16. Note: SP and TP respectively express the starting points and the terminal points of four α-helical fragments.

	Name	SP	Sequences	TP
Helix-1				
	HIL-2	12	LQLEHLLLDLQMIL	25
	HIL-4	5	ITLQEIIKTLNSLT	18
	HIL-16	7	STDSAASASAASDV	20
Helix-2				
	HIL-2	55	HLQCLEEELKPLEEVLN	73
	HIL-4	41	EKETFCRAATVLRQFYS	57
	HIL-16	45	SLEGGKGSLHGDKPLTI	61
Helix-3				
	HIL-2	84	DLISNINVIVLELKGSE	100
	HIL-4	70	AQQFHRHKQLIRFLKRLDRNLWGLA	94
	HIL-16	72	QSETVQPGDRIIQLGGTAMQGLTRF	96
Helix-4				
	HIL-2	114	IVEFLNRWITFCQSIIST	131
	HIL-4	109	LENFLERLKTIMREKYSK	126
	HIL-16	109	PVIIVIRRKSLQSKETTA	126

the Kollmann all-atom force field in SYBYL 6.3. A cutoff of 0.8 nm was used, and dielectric constant was set at 5.0 and was dependent on the distance[13].

According to the crystal structure of HIL-5, a dimeric model of HIL-16 was built end to end of the HIL-16 monomer using Biopolymer module. On the basis of the homodimer of HIL-16, the tetrameric model of HIL-16 was constructed by back to back link of two disulfide bridges (Cys31-Cys31).

Molecular modeling of a complex with HIL-16 and CD4 In the same way, the molecular models of dimeric and tetrameric complexes with HIL-16 and CD4 were built using the Biopolymer modules within SYBYL software. First the dimeric complex with HIL-16 and CD4 were generated on the basis of HIL-16 dimer and known CD4 dimer (PDB code file 1wio). Subsequently, the tetrameric complex with HIL-16 and CD4 were constructed based on this dimeric complex by two disulfide bonds (Cys31-Cys31).

RESULTS

Fig 1 shows that human interleukin-16 has a high homology with HIL-2 and HIL-4. Fig 2 displays the sequence homology of the four helical regions of HIL-16, HIL-2, and HIL-4, which possess a high homology towards each other. This is useful to design and ensure the probability of helical fragments. According to the crystal coordinates of known helical regions of HIL-2 and HIL-4, the four-helix amino acid residues were confirmed and listed in Tab 1. The residue fragments of helix-1, helix-2, and helix-4 of HIL-16, HIL-2, and HIL-4 in Tab 1 are consistent with those in Fig 2. However, the third helical regions of the three interleukins in Tab 1 are different from those in Fig 2 because the third helix length of HIL-2 from PDB is shorter than that of HIL-4. Therefore, the structure model of HIL-16 is actually built on the basis of the data of Tab 1, especially the helical regions.

Molecular modeling of HIL-16 and its polymers Structural analysis of HIL-16 model showed that there were five helical domains, such as helix-1 (Thr8 \ | Ser18), helix-2 (Leu46-Gly51), helix-2′ (Gly55-Val62), helix-3 (Val76-Thr94), and helix-4 (Val 110-Ala127), and other secondary structural elements in it. HIL-16 practically belongs to a four-helical bundle short-chain chemokine family because the unstable activity of Ser53-Leu-His motif causes helix-2 to break into two parts, helix-2 and helix-2′. Only one cysteine residue exists in IL-16, which is important to form tetrameric structure of HIL-16.

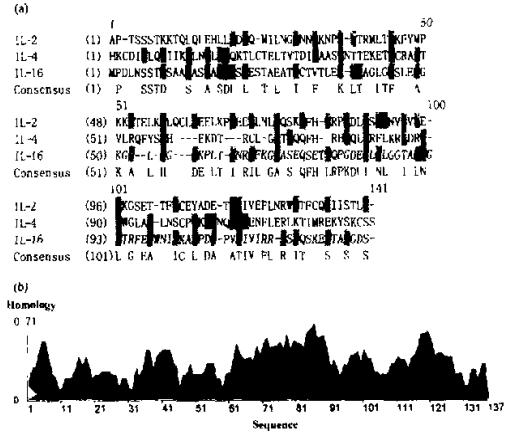

Fig 1. The homology comparison of human interleukin-16 with human interleukin-2 and human interleukin-4. (a) The sequence alignments of HIL-16 with HIL-2 and HIL-4. (b) The concentration distributing of the homology sequences of these interleukins.

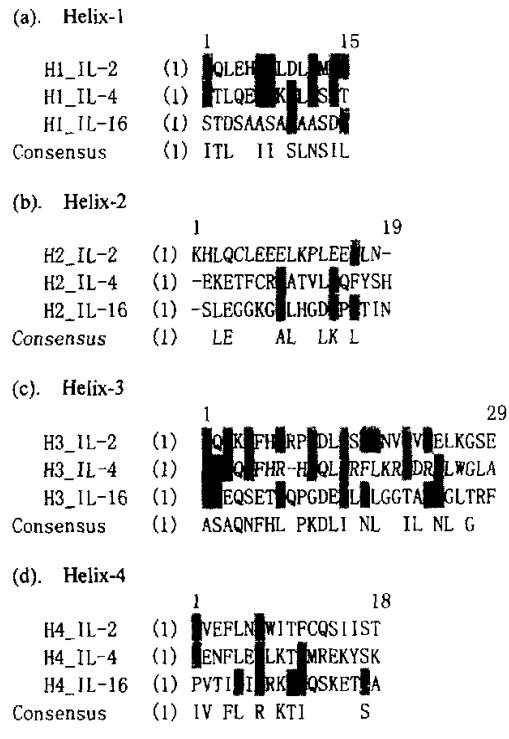

Fig 2. The four helical sequence alignments of HIL-16 with HIL-2 and HIL-4.

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Based on the crystal structure of IL-5 dimer, the homodimer model of IL-16 was constructed where the four helices are located end to end and C-termini to C-termini. This dimeric model of HIL-16 is built by end to end replication of HIL-16 monomer, which is similar to that of HIL-5. This model is in the axis of symmetry, and amino-terminal and carboxyl-terminal are situated on the same side, and the only cysteine is on the opposite side. Structural analysis suggests that there are some hydrophobic interactions between the AB loop, helix-2 and the CD loop of one strand of HIL-16 and those of another strand of HIL-16. And the carboxyl-terminal residue Asp129 of one strand of HIL-16 forms double hydrogen bonds with two amino-terminal residues (Leu4 and Asn5) of another strand, respectively.

A disulfide-linked tetrameric structural model suggests that HIL-16 forms a homotetramer with 130 amino-acid residues in each chain and is linked by two disulfide bridges (Cys31-Cys31). There is a hydrogen bond between the AB loop of one stand and the CD loop of another, which exists between the residue Lys37 and Asn100, and there is some hydrophobic interaction among the CD loops (Phe96, Try99, etc).

Molecular modeling of a complex with HIL-16 and CD4 glycoprotein Fig 3 shows a four-member complex with a homodimer of HIL-16 and the CD4 dimer, which displays a model with an axis of symmetry. Here, the dimeric complex with HIL-16 and CD4 reveals that the carboxyl-terminal of HIL-16 interacts with the V4 region of CD4, which includes four HIL-16 residues (Glu123, Thr125, Asp129, and Ser130) and four CD4 residues (Ser350, Gly351, Gln352, and Val353). The C-terminal acid residues of HIL-16 interact with a Ser350-Gly-Gln-Val353 motif of CD4 by hydrogen bonds. The residue Glu123 respectively forms a hydrogen bond with Gln352 and Val353 of V4 region. Similarly, the residue Ser350 of V4 region forms two hydrogen bridges with Thr125 and Asp129 of HIL-16, respectively.

Fig 4 shows a tetrameric complex with HIL-16 and CD4 by forming two disulfide bridges between the two dimeric complexes (Cys31-Cys31) in the same way as HIL-16 tetramer. The tetrameric complex shows a center symmetry model, where the tetrameric HIL-16 is located in the inner area of the complex and the two dimeric CD4 molecules surround the HIL-16 nucleus in a crossing manner. The two HIL-16 dimers are parallel back to back with two disulfide bridges with respect to C- and N- termini, and N-termini and C-termini of the two dimmers are situated at the contrary side. Additionally, there are some interactions between two strands of HIL-16 and the V1 regions of dimeric CD4 structure. Besides the hydrogen bond between Ala40 and Ser39 of HIL-16, there is another type of hydrogen bond between the residue Asp53 of one V1 region and Ser60 of another V1 region. This is different from the tetrameric structure of HIL-16, which only contains one type of hydrogen bond between Lys37 of one strand and Asn100 of another. These results prove that HIL-16 plays an important role in the interaction of a tetrameric structure with its receptor, CD4 tetramer, especially in the cellular immune response.

DISCUSSION

CD4 is a coreceptor in the cellular immune response. It increases the avidity of association between a T cell and an antigen-presenting cell by interacting with non-polymorphic portions of the complex between class II major histocompatibility complex (MHC) and T cell receptor (TCR) molecules. And it contributes directly to signal conduction through its cytoplasmic association with the lymphocyte kinase Lck. CD4 also serves as the high-affinity receptor for cellular attachment and entry of the human immunodeficiency virus (HIV). The extracellular portion of CD4 comprises of four immunoglobulin-like domains whose structures have a hinge-like variability at the V1/V2 to V3/V4 junction that might be important in immune recognition and HIV fusion, and a common dimeric association through V4 domains. Wu *et al* suggest that the dimers may have relevance as mediators of signal conduction in T cells[13]. IL-16 usually plays a role in a tetrameric structure despite its tertiary structure unknown. As it is a chemoattractant factor for all $CD4^+$ leukocytes and is a competence growth factor for $CD4^+$ T cells, IL-16 might play a role in accumulation and activation of $CD4^+$ immune cells at sites of inflammation.

The studies above have shown that HIL-16 can exist in a center symmetry tetrameric complex model and may possess some biological activities (such as anti-HIV activity). Interleukin-16 and HIV-1 envelope glycoprotein gp120 share a common receptor, CD4 antigen. The activity of IL-16 is absolutely dependent upon the presence of membrane-expressed functional CD4 based on studies reported. Competition studies indicate that the IL-16 binding site on CD4 may be in close vicinity to the epitope recognized by the anti-CD4 mAb OKT4 in the V4 domain, whereas HIV-1 gp120 binds the V1 region of CD4[7]. Mashikian's studies indicate the existence of

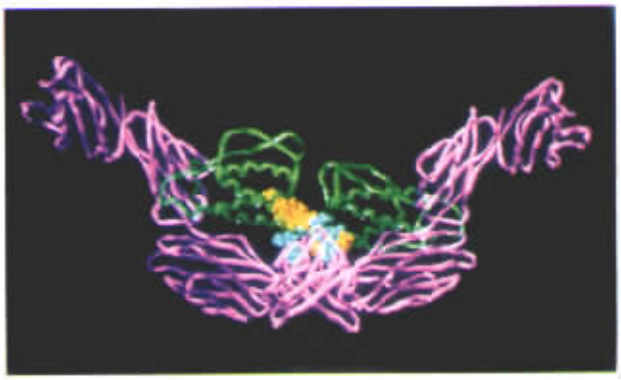

Fig 3. A dimeric complex of HIL-16 and CD4 glycoprotein. The mainchain of human CD4 and HIL-16 separately appear as purple and green shaded ribbons. HIL-16 is composed of five helices, three loops and C-/N- terminal domains. The active sites appear as orange and green full-space balls; the orange display the residues of CD4, Ser350-Gly-Gln-Val; the green display the residues of HIL-16, Glu123, Thr125, Asp129, and Ser130.

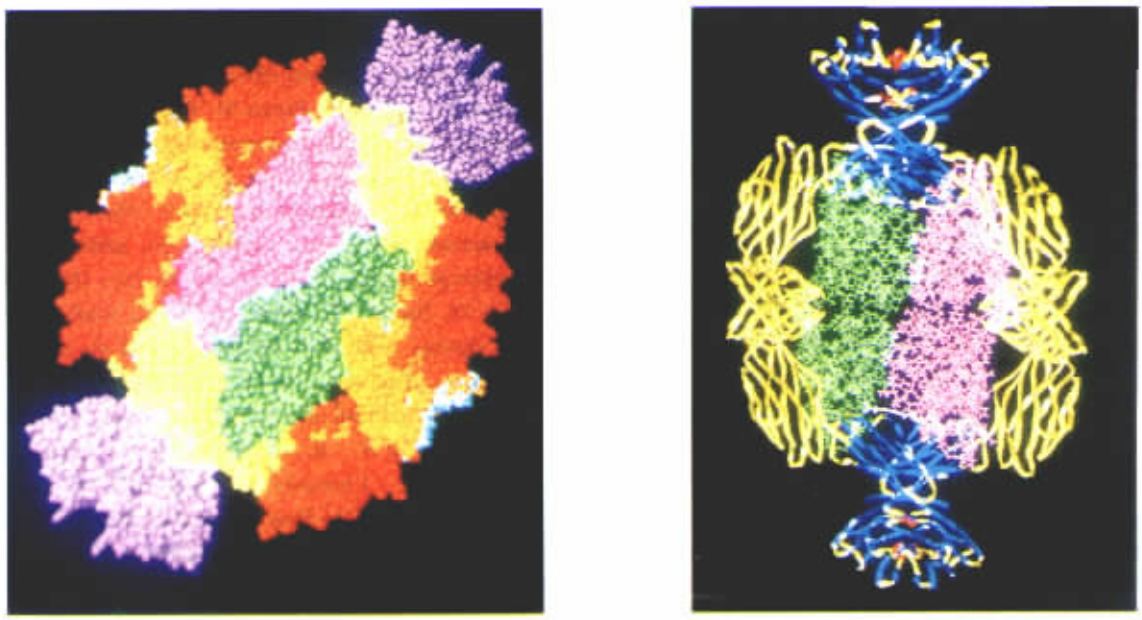

Fig 4. A tetrameric complex of HIL-16 and CD4 glycoprotein. (A). These proteins are displayed by colored full-space balls. HIL-16 dimers are colored purple and green. The four domains of CD4 are colored violet (D1), yellow (D2), red (D3), and orange (D4). (B). HIL-16 dimers are displayed by purple and green lines. The four domains of CD4 are displayed by yellow or blue shaded ribbons. The disulfide bridges are white.

reciprocal receptor cross-desensitization between CD4 and CCR5 induced by two proinflammatory cytokines, IL-16 and MIP-1β, and suggest a selective relationship between the two receptors[15]. Moreover, CCR5 is a coreceptor for immunodeficiency virus' entry into the host cell and the HIV virus binding CD4 can induce some conformational changes in gp120 glycoprotein, leading to the exposure of the specific chemokine receptor-binding site of immunodeficiency virus subsequently. Furthermore, the apparent affinity of the interaction between gp120 and CCR5 is lower in the absence of insoluble CD4. Well then, how about the relation between human CCR5 and HIL-16?

Kwong *et al* have reported that the interaction between CD4 and CCR5 can be observed in the absence of gp120[4]. And our molecular modeling of CCR5 complex with gp120 and CD4 shows that Met 1 of human CCR5 contacts Arg56 of CD4 in electrostatic interaction and Gln4 interacts with the critical CD4 residues, Arg58 and Arg59[14]. On the other hand, our results are identical with the views of Baier *et al*[7] who report that CD4 can contact CCR5 and HIL-16 at the different position despite CD4 glycoprotein being the common receptor of CCR5 and IL-16. So is there some direct or indirect interaction between CCR5 and human interleukin-16? We failed to construct the complex model with CD4/HIL-16 and CD4/gp120/CCR5 by CD4 linkage because of a huge spacial block and a limiting calculating capability of workstation. Therefore, it was supposed that HIL-16 could not directly interact with CCR5, which implied that

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HIL-16 might indirectly affect the activity of CCR5. The affinity of the interaction between gp120 and CCR5 was lower along with weaker concentration of CD4, which was the common receptor of CCR5 and HIL-16. Thus, it was deduced that the concentration of soluble CD4 dropped when human IL-16 competed to contact CD4 glycoprotein, which could bring about a lower-affinity of the interaction between gp120 and CCR5. From the results above, it is inferred that HIL-16 has an anti-AIDS activity, maybe due to the lower level of CD4, which is supported by Theodore *et al*[6].

Although HIL-16 has an anti-HIV activity in the tetrameric structure, it is not clear how it interact with its receptor and whether HIL-16 first forms a tetramer then comes in contact with four CD4 molecules? Our studies above reveal an interaction mechanism in the cellular immune response which implies that HIL-16 first forms a homodimer, then contacts CD4 dimer and forms a dimeric complex with HIL-16 and CD4. Subsequently, the tetrameric complex is constructed of two dimeric complexes with two disulfide bridges between one HIL-16 and another. Finally, HIL-16 plays an important role in a tetrameric complex with CD4. This is supported by the studies of Wu *et al*, where dimeric association and segmental variability exist in the structure of human CD4[12]. There is a key cysteine residue, Cys31, in interleukin-16. It plays a linking role in polymer formation. In the complex model of HIL-16 dimer and CD4 dimer, this residue still exposes itself to the environment, for it is at the loop of interleukin-16, which is propitious to the formation of the tetrameric complex model of HIL-16 and CD4 by two disulfide bridges. Namely, Cys31 greatly contributes to the formation of the tetrameric complex model. The action mechanism of HIL-16 is only a theoretic deduction, which needs further pharmacological verification.

In summary, the anti-AIDS activity of HIL-16 can be shown by CCR5 competing for CD4 and resulting in descrease of CD4 with reduced effect on CCR5. On the other hand, as it is a chemoattractant factor for all $CD4^+$ leukocytes and is a competence growth factor for $CD4^+$ T cells, IL-16 play a role in accumulation and activation of $CD4^+$ immune cells at the sites of inflammation.

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人白介素 16 与 HIV-1 的 CD4 受体的相互作用

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关键词 分子结构；白介素-16；CD4 抗原；计算机辅助设计；蛋白质构象

目的：研究人白介素-16 和 HIV-1 病毒受体 CD4（T 淋巴细胞分化抗原）的作用机理. **方法**：人白介素-16 的结构保守区由 SYBYL 软件中的 Biopolymer 模块建立，其非保守区由 LOOP SEARCH 方法建立. **结果**：人白介素-16 首先形成二聚体，然后与 CD4 的二聚体进一步形成 HIL-16 与 CD4 的复合物二聚体. 接着，该复合物二聚体通过二硫键（Cys31-Cys31）形成 HIL-16 与 CD4 复合物的四聚体. **结论**：该相互作用模型有助于推测白介素-16 的作用机制，也有益于全新抗艾滋病药物的合理设计.

（责任编辑 朱倩蓉）