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Computational prediction of MHC Ⅱ-peptide ligands binding specificities by AUC Optimized Gibbs

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Abstract: In the design of peptide-based or other defined antigen-based vaccines, it is important to know which fragments of pathogen-derived proteins would bind to the MHC Ⅱ molecules. Most studies of the MHC Ⅱ epitope prediction rarely gave the quantitative analyses of binding specificities. So the accuracy of these models still needs to be improved. AUC Optimized Gibbs (AOG) method uses the homology reduced AUC, rather than the relative entropy to guide the sampler. It makes both the positive and negative information of the samples be incorporated into the model. AOG achieves average AUC values of 0. 771 and 0. 713 on the ten original and homology reduced HLA-DR4 (B1 * 0401) epitope benchmarks, which are better than 0. 744 and 0. 673 by the Gibbs sampling method. In the quantitative IEDB MHC-Ⅱ benchmarks, AOG achieves an average AUC value of 0. 766, compared to 0. 718 by the TEPITOPE. A detailed inspection of information extracted from HLA-DR4 (B1 * 0401) data allows the identification of positions with obvious specificities, i. e. , P1, P4, P6 and P9 positions, which have distinct influence on the MHC-peptide binding.

Key words: Gibbs sampling method; epitope; MHC Ⅱ molecules; reduced homology

0 Introduction

Recently there has been constant concern about the rules for the binding of peptides to MHC molecules. The MHC molecules deliver fragmented pieces of an antigen protein on the host cell′s surface to the cytotoxic T cell (Tc) or the helper T cell (Th), giving rise to their development and activation. It is important to know which peptide fragments of pathogen-derived proteins most probably bind to a certain MHC-molecule. The MHC Ⅰ binding groove is closed, which tends to bind short peptides of 8-10 amino acids by both ends. But the MHC Ⅱ binding groove is open, which makes the length of the peptides bound by MHC Ⅱ molecules unconstrained. And relative to the MHC Ⅰ molecules, the binding pockets of MHC Ⅱ molecules are more permissive in the accommodation of amino acids. The two obstacles greatly affect the performance of MHC Ⅱ binding peptide prediction.

On the opinion of the IBS hypothesis[1], for

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most peptides, each side chain of the peptide sequence contributes a certain amount to the stability of binding peptides to MHC Ⅱ molecules; and the MHC Ⅱ-peptide ligands binding affinity is independent of the peptide sequence. The influence of residues at each position in the peptide sequence on the binding affinity can be considered independently. Based on this hypothesis, some linear models, additive PLS method[2], stabilized matrix method[3], Gibbs sampling method[4] and SMM-align method[5] have achieved reasonable performance.

AUC Optimized Gibbs (AOG) method used in the study is a changed version of Gibbs sampling method. The Gibbs sampling method was applied to predict class Ⅰ and class Ⅱ epitopes[4]; Whereas, the relative entropy is used to guide the sampler, resulting in that only binding peptides are used for training, and non-binding peptides are discarded. This leads to a low efficient use of the training data. In the study, the homology reduced self-fitting AUC is used to guide the sampler, resulting in that both the positive and negative information could be incorporated into training the sampler. In the HLA-DR4 (B1 * 0401) epitope benchmark and quantitative IEDB benchmark, the AOG algorithm is used as well as Gibbs sampling method[4] and TEPITOPE[6]. Through reduction of the noise from the experimental data using the AOG method, MHC Ⅱ binding specificities are computationally predicted, and the profile of the MHC Ⅱ molecule interacting with its peptides is analyzed from the results of the algorithm. The processing of class Ⅱ epitopes as well as design of better peptide vaccine can be understood well.

1　Methods and materials

1.1　Training and testing data

1.1.1　Training datasets for HLA-DR4 (B1 * 0401)　462 Binding peptides and 177 non-binding peptides that have interacted with the HLA-DR4 (B1 * 0401) constitute the HLA-DR4 (B1 * 0401) training set. The binding peptides are extracted from SYFPEITHI[7], which have been described by Nielsen, *et al*[4]; The non-binders are extracted from MHCBN[8], which have been described by Murugan, *et al*[9]. Both the training set and the evaluation set contain two columns. The first column gives the peptide sequence, and the second one gives the IC_{50} log-transformed binding affinity pIC_{50}, p$IC_{50}=1-\log(IC_{50}/(\text{nmol}\cdot\text{L}^{-1}))/\log 50\,000$[4]. This set is referred to as DR4-training.

1.1.2　Testing datasets for HLA-DR4 (B1 * 0401)　HLA-DR4 (B1 * 0401) benchmarks are the same benchmarks used by Nielsen, *et al*[4]. They consist of ten datasets; and eight of ten datasets are downloaded from MHCbench (http://www.imtech.res.in/raghava/mhcbench), the rest two are Southwood and Geluk datasets[4]. The same threshold to determine binders and non-binders as Nielsen, *et al.* (2004)[4] is used in study in this paper. For the 8 MHCbench datasets, peptides with a binding value of non-zero are defined as binders and all other peptides are defined as non-binders. For the Southwood and Geluk datasets, an affinity of 1 000 nmol/L is taken as the threshold, which is peptides with an associated pIC_{50} larger than 0.36 are defined as binding peptides. The 10 benchmarks are through homology reduction, which ensures that no peptide in the benchmarks has a match in the training set with more than 7 identical amino acids over an alignment of 9 amino acids. Tab. 1 shows a summary of the original and the homology-reduced benchmark datasets, respectively.

1.1.3　IEDB HLA-DR restricted testing datasets　A quantitative IEDB HLA-DR restricted peptide-binding data for each HLA-DR alleles partitioned into 5 datasets using the method described by Nielsen, *et al*[10]. Each dataset and its corresponding partition are available online at http://www.cbs.dtu.dk/suppl/immunology/NetMHC-2.0.php.

Tab. 1　Description of HLA-DR4 (B1*0401) testing datasets

Set	original			homology-reduced		
	binders	non-binders	total	binders	non-binders	total
Set 1	694	323	1 017	248	283	531
Set 2	381	292	673	161	255	416
Set 3a	373	217	590	151	204	355
Set 3b	279	216	495	128	197	325
Set 4a	323	323	646	120	283	403
Set 4b	292	292	584	120	255	375
Set 5a	70	47	117	65	45	110
Set 5b	48	37	85	47	37	84
Geluk	16	6	22	15	6	21
Southwood	22	83	105	19	80	99

1.2　AOG algorithm

1.2.1　Core nonamers filter　There is a binding core in the binding peptides to MHC Ⅱ molecules, which is approximately 9 amino acids long. This binding core reveals some distinctions from randomness in the frequency of amino acids (i.e., the background in the SWISS-PROT database[11]). And a statistically significant alignment is likely to grasp such distinctions[12]. On the basis of this idea, the algorithm samples possibly ungapped alignment from *n* peptide sequences (*n* is the number of binding peptides in the training set). Because nearly all the binding peptides have a hydrophobic residue (F, I, L, M, V, W, Y) at P1 position[13], the sampling restricts to the ungapped nonamers that have a hydrophobic residue at P1 position. The size of the search space could be greatly reduced, e.g., given a binding peptide 'GNKLCALLYGDAEKP', nonamers for selecting are 'LCALLYGDA' and 'LLYGDAEKP', and the other candidates that do not have a hydrophobic residue at P1 are discarded.

1.2.2　Sequence weights　Closely related sequences carry similar information, and a large set of them make the raw amino acid frequencies calculation badly biased. Hobohm 1-like algorithm[14] is used for clustering the sequences and a sequence identity of 62% is used as the cluster threshold, e.g., if sequence A has 6 (≥9×62%) amino acids identical to the sequence B in their aligned positions, A and B are clustered, and are assigned a weight 1/2. If C has 6 amino acids identical to sequence A or B in their aligned positions, A, B and C are clustered and assigned a weight 1/3.

1.2.3　Scoring matrix calculation　Pseudo-frequency method is used for estimating the frequency of amino acids for low counts[4]. For an alignment, the pseudo-count frequency of amino acid *i* at position *j* is

$$g_{ij} = \sum_{i'} \frac{f'_{i'j}}{P_{i'}} q_{ii'} \tag{1}$$

Where $f'_{i'j}$ is the observed frequency of amino acid i' at position j. $P_{i'}$ is the background frequency of amino acid i' in the SWISS-PROT database[11]. $q_{ii'}$ is calculated as

$$q_{ii'} = Q_{i'} Q_i \mathrm{e}^{\lambda_u S_{i'i}} \tag{2}$$

Where $Q_{i'}$ is the observed frequency of amino acid i' in the alignment and λ_u is a random scale number (2 by default); $S_{i'i}$ is the observed probability of occurrence for i and i' amino pair from the Blosum62 substitution matrix[14].

The effective amino acid frequency is

$$f_{ij} = \frac{\alpha \cdot f'_{ij} + \beta \cdot g_{ij}}{\alpha + \beta} \tag{3}$$

Where α is the number of clusters, β is the weight on the pseudo-count correction. A too great value of β would reduce the sensitivity of scoring prediction matrix. The score of the amino acid i in position j is computed as log-odds ratios:

$$\log(f_{ij}/P_i)$$

Since different positions have different impact on the binding peptides and MHC Ⅱ molecule interaction, i. e., anchor positions are more important than ordinary positions. The position-determined parameter μ_j is introduced; And the final 9×20 scoring matrix $\boldsymbol{M}$ is calculated as

$$m_{ij} = \sum_{j=1}^{9} \mu_j \log(f_{ij}/P_i) \tag{4}$$

The score of a nonamer subpeptide is the sum of all the scores of amino acids in the nine positions. And the score of a peptide is the highest score of all nonamer subpeptides in the peptide sequence.

1.2.4　AUC calculation　The receiver operator characteristics (ROC) curve is a two-dimensional curve; the false positive rate of the prediction is plotted on the X axis and the true positive rate of the prediction is plotted on the Y axis over a continuous range of cut-off values from high to low. The AUC value is the area under the ROC curve; it reflects the ability of a model that can tell a randomly chosen positive instance from a randomly chosen negative one[15]. In the study, ROC analysis is used for measurement of the ability of different models to identify the MHC class Ⅱ epitopes. Homology reduced AUC is calculated on the Hobohm 1-like[14] homology-reduced training dataset. This implement ensures that there are not two peptides in the training set that have over nine identical continuous amino acids.

1.2.5　AOG algorithm　(i) raw alignment: a new starting point is chosen randomly in a peptide sequence. The random alignment is run for 5 000 times to reach a relatively high-AUC alignment. Since the alignment space has a very large number of local maxima with close to identical prediction accuracy, this procedure is repeated 100 times with different initial configurations. The probability of accepting a new alignment in the sampling is calculated as:

$$P = \min\left[1,\ e^{(AUC_{\text{new}} - AUC_{\text{old}})/T}\right] \tag{5}$$

Where T is a scalar. (ii) Precise alignment: for the starting point of the binding peptide voted by a majority of the 100 alignments in (i), twice selecting probabilities of other starting points are used. The precise alignment is run for 100 000 times to reach the final optimal alignment. (iii) The two factors that influence the performance of the scoring matrices are the weight β in the effective amino acid frequency calculation and the position specific weight μ_j. A two-stage Monte Carlo method[16] is implemented, alternately shifting μ_j in Eq. (4) and β in Eq. (3) to optimize these parameters.

In (i), the scalar T implicit in Eq. (5) is set to 0.001, that reduces the probability of accepting unfavorable alignment; In (ii), the scalar T is set from 0.1 to 0.001, that gradually reduces the probability of accepting unfavorable alignment; In (iii), the scalar T is set to 0.001, that reduces the probability of accepting unfavorable score matrices. The altered T in (ii) makes the probability P unfixed and accordingly guarantees the alignment chain irreducible and aperiodic (and thus ergodic)[16].

2　Results

2.1　MHC Ⅱ (HLA-DR4 (B1 * 0401)) weight matrix extraction

Using HLA-DR4 (B1 * 0401) training data DR4-training, an AUC-guided iterative training process is employed to get the optimal alignment, parameters and the corresponding scoring matrix. The final scoring matrix for HLA-DR4 (B1 * 0401) is shown in Fig. 1. Each item m_{ij} of the scoring matrix $\boldsymbol{M}$ respectively corresponds to a kind of amino acid i in a sequence position j, and the sum of these scores is the predicted binding affinity. Hence, the scoring matrix $\boldsymbol{M}$ can be seen as the impact of each amino acid in sequence positions on the binding affinity. The height of the symbol of the amino acid i is proportional to the absolute value of m_{ij}. The upside or upside-down symbol represents the positive or negative sign of m_{ij} respectively. The colors of amino acid symbols represent their physicochemical characteristics, i. e., black, neutral and hydrophobic; blue, basic; green, neutral and polar; red, acidic. (due to print limit, here using different shades for demonstration)

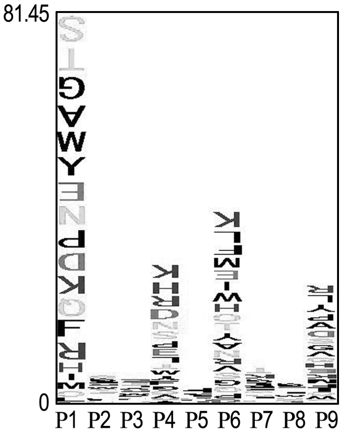
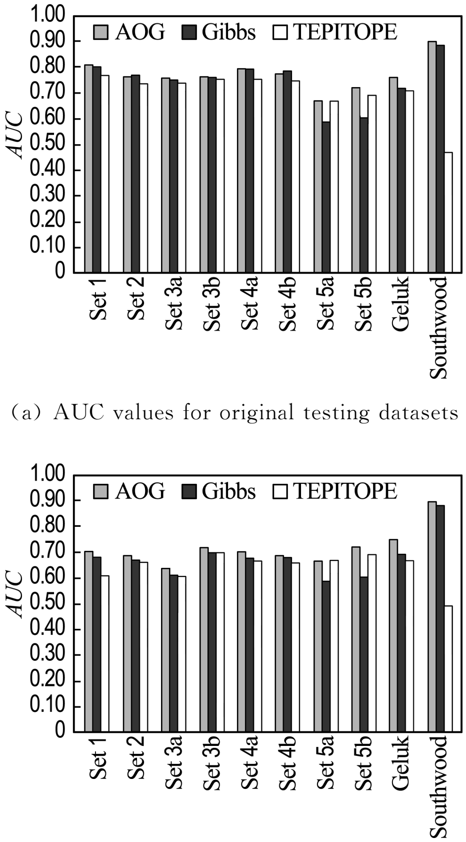


Fig. 1 The weight coefficients of amino acids in HLA-DR4 (B1＊0401) peptides

Each symbol column corresponds to a sequence position between P1 and P9.

2.2 Results for the HLA-DR4 (B1＊0401) data

The performance of the AOG method, Gibbs sampling method and TEPITOPE are compared on the HLA-DR4 (B1＊0401) benchmarks. The results of Gibbs sampler are calculated with the weight matrix offered by Nielsen; this weight matrix is trained with the positive samples of the DR4-training; the results of TEPITOPE are gained with the weight matrix from ProPred[6]. The AUC value of each method on the 10 benchmarks is illustrated in Fig. 2(a) and Fig. 2(b). It is observed that AOG gives a better performance than the Gibbs sampler and TEPITOPE. The average AUC values on the original and homology reduced benchmarks are 0. 771 and 0. 713, respectively. The average AUC values are 0. 744 and 0. 673 for the Gibbs sampler and 0. 702 and 0. 667 for TEPITOPE.



(a) AUC values for original testing datasets

(b) AUC values for homology reduced testing datasets

Fig. 2 Prediction performance of various methods on the HLA-DR4 (B1＊0401) benchmarks

2.3 Results for quantitative IEDB HLA-DR data

The predictive performances of AOG and TEPITOPE on the quantitative IEDB benchmark datasets are estimated using five-fold cross-validation. In each cross-validation, 1/5 of the data are left out for evaluation and the remaining 4/5 are used for an alternating training. The predictive performances of AOG and TEPITOPE on the 11 HLA-DR allele benchmarks are shown in Tab. 2. The predictive performances of AOG method and TEPITOPE are in terms of AUC values, using a binding affinity threshold of 500 nmol/L. The results of TEPITOPE are obtained with the use of the scoring matrix from ProPred[6]. Since ProPred offers scoring matrices for only 11 alleles, the rest 3 alleles are not included in the table. It is clear that AOG method has a higher performance than TEPITOPE for most alleles (10/11). Only for one allele (DRB1 * 0404) does the TEPITOPE outperform AOG method.

Tab. 2 Predictive performances of AOG and TEPITOPE for the 11 HLA-DR alleles in the quantitative IEDB benchmark datasets

Allele	Total	Binders	Predictive performances	
			TEPITOPE	AOG
DRB1 * 0101	5 166	3 505	0.720	0.754
DRB1 * 0301	1 020	276	0.664	0.769
DRB1 * 0401	1 024	510	0.716	0.781
DRB1 * 0404	663	386	0.770	0.752
DRB1 * 0405	630	426	0.759	0.792
DRB1 * 0701	853	498	0.761	0.773
DRB1 * 0802	420	148	0.766	0.801
DRB1 * 01101	950	429	0.721	0.770
DRB1 * 01302	498	199	0.652	0.760
DRB1 * 01501	934	450	0.686	0.741
DRB5 * 0101	924	478	0.680	0.733
Ave			0.718	0.766

3 Discussion

As shown in Fig. 1, the height of each amino acid symbol is proportional to its absolute score, which is the contribution of the amino acid in a sequence position to the MHC-peptide binding affinity, and the height of all amino acid symbols stacked on each position along P1-P9 is proportional to the sum of corresponding absolute scores for the 20 possible amino acids on the position, which is the contribution to the binding affinity. The positions in core region of the peptides have distinct specificities, i. e., P1, P4, P6 and P9 positions have distinct influence on the HLA Ⅱ-peptide binding.

For the purpose of interpreting the amino acid characteristics in HLA Ⅱ-peptide primary positions that are presented in Fig. 1, the crystal structures of DRB1 * 0401 (PDB id: 1J8H, 1D5Z, 1D6E, 2SEB, 1D5M, 1D5X) are used to find amino acids that make nonbonding contact with the peptides (i. e., two residues are defined to be nonbonding contact if the distance of two atoms of these residues is smaller than 0.4 nm)[17]. Tab. 3 lists the amino acids of α-chain and β-chain of DRB1 * 0401 nonbonding contact with the peptides.

Tab. 3 The amino acids of the HLA-DR4(B1 * 0401) molecule nonbonding contact with the peptides

position	chain	amino acids
P1	α-chain	Ile7 Phe24 Ile31 Phe32 Trp43 Ala52 Ser53 Phe54
	β-chain	Asn82 Val85 Gly86 Phe89
P2	α-chain	Phe24
	β-chain	Thr77 Tyr78 His81 Asn82
P3	α-chain	Gln9 Phe22 Phe54 Gly58 Ala59 Asn62
	β-chain	Tyr78
P4	α-chain	Gln9 Asn62
	β-chain	His13 Phe26 Asp28 Gln70 Lys71 Ala74 Tyr78
P5	α-chain	Gly58 Ala61 Asn62 Val65
	β-chain	His13 Gln70 Lys71
P6	α-chain	Glu11 Asn62 Val65 Asp66 Asn69
	β-chain	Val11 His13 Lys71
P7	α-chain	Val65 Asn69
	β-chain	Tyr30 Tyr47 Trp61 Leu67
P8	α-chain	Val65 Ala68 Asn69 Ile72
	β-chain	Tyr60 Trp61
P9	α-chain	Asn69 Ile72 Met73 Arg76
	β-chain	Glu9 Tyr37 Asp57 Tyr60 Trp61

Neutral amino acids are colored black, electropositive and basic amino acids are colored blue, and electronegative and acidic amino acids are colored red (due to print limit, here using different shades for demonstration).

P1 position: Residues of the HLA DRB1 * 0401 molecule that make nonbonding contact with residues of peptides in P1 position are Ile7, Phe24, Ile31, Phe32, Trp43, Ala52, Ser53, Phe54 in the α-chain and Asn82, Val85, Gly86, Phe89 in the β-chain (see Tab. 3). It is found that, the P1 pocket is shaped by conserved aliphatic amino acids (Ileα7, Ileα31, Serα53, Alaα52, Valβ85, Glyβ86) and aromatic amino acids (Pheα24, Pheα32, Pheα54, Trpα43, Pheβ89) and represents a highly hydrophobic environment. Jardetzky′s single residue substitution experiment[13] demonstrates that the main determinant of binding is a large pocket that accommodates a hydrophobic or aromatic amino acid side chain near the N terminus of the peptide (the P1 position). From Fig. 1, the following can be figured out: (i) The sum of absolute values in P1 position is significantly larger than that of any other position, indicating that P1 position has the highest influence on the binding affinity; (ii) Polar amino acids have negative scores in P1, which indicates that polar amino acids are unfavorable to the binding; Hydrophobic amino acids have positive scores in P1, which indicates that these hydrophobic amino acids are favorable to the binding; (i) and (ii) are in accordance with the Jardetzky′ s conclusion[13]. (iii) Stable amino acid residues F, W and Y have much higher scores than less stable amino acid residues I, L, M and V, which indicates that stable amino acid residues are more favorable to the binding; this result is in accordance with the Tobita′ s conclusion[18]—Difference in stability of amino acids in P1 closely correlates with the binding affinity.

P4 position: Residues of the HLA DRB1 * 0401 molecule that make nonbonding contact with residues of peptides in P4 position are Gln9, Asn62 in the α-chain and His13, Phe26, Asp28, Gln70, Lys71, Ala74, Tyr78 in the β-chain (Tab. 3). The electronegative and acidic amino acids Aspβ28 and electropositive and basic amino acids Hisβ13 and Lysβ71 endow the P4 pocket polar binding characteristics; Previous studies[19] on the HLA-peptide affinity have shown that the positively charged Lysβ71 can make direct contact with side-chain residues from the antigenic peptide; Lysβ71 makes this pocket tend to have a high affinity for negatively charged or uncharged polar amino acids, whereas disfavors positively charged amino acids (like Lys). This is an approval of the algorithm in P4 position: in Fig. 1, negatively charged amino acids Asp and Glu have the highest positive scores, whereas electropositive and basic amino acids Lys, Arg and His have the lowest negative scores. From Fig. 1, it is also found that bulky amino acids Phe and Trp also have relatively high positive score that may indicate that P4 pocket is a large sized one.

P6 position:Residues of the HLA DRB1 * 0401 molecule that make nonbonding contact with residues of peptides in P6 position are Glu11, Asn62, Val65, Asp66, Asn69 in the α-chain and Val11, His13 and Lys71 in the β-chain (Tab. 3). As indicated by the amino acid symbol height stacked in P6 position in Fig. 1, P6 is a major anchor and inhibitory residue position. The electronegative and acidic amino acids Gluα11, Aspα66 and electropositive and basic amino acids Hisβ13 and Lysβ71 endow the P6 pocket a polar interface; The experimental results[20] have shown that this pocket favors the binding of medium sized (like Met, Leu and Ile) or polar amino acid residues. In the scoring matrix (Fig. 1), the negatively charged amino acids Asp and polar amino acids Asn, Ser and Thr have positive scores, which may be beneficial to the binding affinity.

P9 position:Residues of the HLA DRB1 * 0401 molecule that make nonbonding contact with residues of peptides in P9 position are Asn69, Ile72, Met73, Arg76 in the α-chain and Glu9, Tyr37, Asp57, Tyr60, Trp61 in the β-chain (Tab. 3). As indicated by the amino acid symbol height stacked in P9 position in Fig. 1, P9 is a major anchor and inhibitory residue position. The P9 pocket is shaped by neutral amino acids Tyrβ37 and Tyrβ60 and electronegative and acidic amino acids Gluβ9 and Aspβ57[21]. So the positively charged or polar residues are favored in the P9 pocket. In the scoring matrix (Fig. 1), the positively charged amino acids His and polar amino acids Gly, Ser and Gln have positive scores. It is indicated that these amino acids may enter the inner cavity wall of P9 easily. As an unexpected result, the hydrophobic amino acid Ala has the highest score in the P9 position, which indicates that P9 pocket is a small sized pocket.

4　Conclusion

A method, AUC Optimized Gibbs (AOG) is developed for prediction of peptide binding to MHC Ⅱ molecules. Tests on 10 HLA-DR4 (B1 * 0401) benchmarks and quantitative IEDB HLA-DR benchmark show that AOG is a better predictive method for MHC class Ⅱ epitopes than Gibbs sampling method and TEPITOPE. The positions in core region of the HLA-DR4 (B1 * 0401) peptides have distinct specificities, i. e., P1, P4, P6 and P9 positions have distinct influence on the MHC-peptide binding.

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基于AUC Optimized Gibbs方法的MHC Ⅱ-短肽配体结合特异性预测

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摘要: 在以短肽定义的或以抗原定义的疫苗设计中,识别哪个来自病原体的蛋白质片段会结合MHC Ⅱ分子是个重要问题.多数MHC Ⅱ表位预测的研究很少给出结合特异性的定量分析,所以这些模型的精确度仍然需要进一步提高.AUC Optimized Gibbs(AOG)使用约化同源性的AUC值而不是相对熵来引导采样,使得正样本和负样本的信息都被用于模型的训练.在10个HLA-DR4(B1 * 0401)原测试集和约化同源性测试集的测试中,AOG得到的平均AUC值分别是0.771和0.713,优于Gibbs的0.744和0.673.在定量IEDB的MHC Ⅱ测试集中,AOG得到的平均AUC值是0.766,而TEPITOPE得到的平均AUC值是0.718.从HLA-DR4(B1 * 0401)数据提取的信息可以识别某些有明显特异性的位置,即P1、P4、P6和P9位置,其对MHC-短肽结合有明显的影响.

关键词: Gibbs采样方法;表位;MHC Ⅱ分子;约化同源性

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