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Immunoproteomics Approach for Development of Synthetic Peptide Vaccine from Thioredoxin Glutathione Reductase

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Abstract

Schistosomiasis is the second most widespread human parasitic disease. It is principally treated with one drug, praziquantel, which is administered to 100 million people each year; less sensitive strains of schistosomes are emerging. One of the most appealing drug targets against schistosomiasis is *thioredoxin glutathione reductase* (TGR). This natural chimeric enzyme is a peculiar fusion of a glutaredoxin domain with a thioredoxin selenocysteine (U)-containing reductase domain. Selenocysteine is located on a flexible C-terminal arm that is usually disordered in the available structures of the protein and is essential for the full catalytic activity of TGR. MHC molecules are cell surface proteins, which take active part in host immune reactions and involvement of MHC class in response to almost all antigens and it give effects on specific sites. Predicted MHC binding regions acts like red flags for antigen specific and generate immune response against the parent antigen. So a small fragment of antigen can induce immune response against whole antigen. This theme is implemented in designing subunit and synthetic peptide vaccines. In this study, we analyzed thioredoxin glutathione reductase of *Schistosoma mansoni* and is allows potential drug targets to identify active sites, which form antibodies against or infection. The method integrates prediction of peptide MHC class binding; proteosomal C terminal cleavage and TAP transport efficiency. Antigenic epitopes of thioredoxin glutathione reductase are important antigenic determinants against the various toxic reactions and infections.

Keywords: Schistosomiasis; Immunoproteomics; Thioredoxin glutathione reductase PSSM; SVM

Introduction

Schistosomes are human platyhelminth parasites causing Schistosomiasis, a severe disease still classified among the major causes of mortality in tropical and subtropical countries, affecting more than 200 million people [1]. The only drug employed to fight the disease is praziquantel, whose efficacy is restricted to the adult stages of the parasite and whose mechanism of action is still incompletely clarified [2,3]. Because this drug is administered to 100 million people every year, some less sensitive strains have already been isolated, and given the massive drug administration, resistance might become a serious problem [3]. Because of this, the search for a new drug against Schistosomiasis is a necessity and a priority according to the World Health Organization [4].

Methodology

In this research work antigenic epitopes of antigen protein from thioredoxin glutathione reductase of *Schistosoma mansoni* is determined using the Gomase, Hopp and Woods, Welling, Parker and Wolfenden, antigenicity [5-8]. The *major histocompatibility complex* (MHC) peptide binding of antigen protein is predicted using neural networks trained on C terminals of known epitopes. In analysis predicted MHC/peptide binding of antigen protein is a log-transformed value related to the IC50 values in nM units. RANKPEP predicts peptide binders to MHCI and MHCII molecules from protein sequences or sequence alignments using Position Specific Scoring Matrices (PSSMs). Support Vector Machine (SVM) based method for prediction of promiscuous MHC class II binding peptides. SVM has been trained on the binary input of single amino acid sequence [9-14]. In addition, we predict those MHC ligands from whose C-terminal end is likely to be the result of proteosomal cleavage [15].

Results and Interpretation

We found binding of peptides to a number of different alleles using Position Specific Scoring Matrix. A thioredoxin glutathione reductase antigen protein sequence is 598 residues long, having antigenic MHC binding peptides. MHC molecules are cell surface glycoproteins, which take active part in host immune reactions and involvement of MHC class-I and MHC II in response to almost all antigens. PSSM based server predict the peptide binders to MHC I molecules of thioredoxin glutathione reductase to MHCII molecules of thioredoxin glutathione reductase sequence as H2_Db, I_Ab, I_Ag7, I_Ad, analysis found antigenic epitopes region in thioredoxin glutathione reductase (Table 1 and 2). We also found the SVM based MHCII-IAb; MHCII-IAd; MHCII-IAg7 and MHCII- RT1.B peptide regions, which represented predicted binders from thioredoxin glutathione reductase. The predicted binding affinity is normalized by the 1% fractil. We describe an improved method for predicting linear epitopes (Table 2). The region of maximal hydrophilicity is likely to be an antigenic site, having hydrophobic characteristics, because terminal regions of thioredoxin glutathione reductase is solvent accessible and unstructured, antibodies against those regions are also likely to recognize the native protein (Figures 1-4). It was shown that thioredoxin glutathione reductase is hydrophobic in nature and contains segments of low complexity and high-predicted flexibility. Predicted antigenic fragments can bind to MHC molecule is the first bottlenecks in vaccine design.

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RANK	POS.	N	SEQUENCE	C	MW (Da)	SCORE	% OPT.
8mer_H2_Db	439	AGK	PQLTPVAI	QAG	820.0	15.001	28.58 %
8mer_H2_Db	24	ILF	SKTTCPYC	KKV	884.03	14.29	27.22 %
8mer_H2_Db	224	VTY	LNAKGRLI	SPH	866.07	13.696	26.09 %
8mer_H2_Db	8	DGT	SQWLRKTV	DSA	976.17	13.263	25.27 %
8mer_H2_Db	246	QKV	STITGNKI	ILA	814.92	11.607	22.11 %
8mer_H2_Db	75	VPQ	MFVRGKFI	GDS	979.25	11.583	22.07 %
8mer_H2_Db	241	ITD	KNQKVSTI	TGN	899.04	11.41	21.74 %
8mer_H2_Db	283	FSL	PYFPGKTL	VIG	904.08	11.377	21.67 %
8mer_H2_Db	52	ELD	QLSNGSAI	QKC	770.84	11.253	21.44 %
8mer_H2_Db	398	PQL	SKVLCETV	GVK	860.03	9.948	18.95 %
9mer_H2_Db	189	DRS	KISHNWSTM	VEG	1062.23	25.291	50.22 %
9mer_H2_Db	152	GLG	GTCVNVGCI	PKK	847.0	16.502	32.76 %
9mer_H2_Db	527	LVC	RKSDNMRVL	GLH	1100.3	13.709	27.22 %
9mer_H2_Db	539	GLH	VLGPNAGEI	TQG	850.97	12.87	25.55 %
9mer_H2_Db	500	DIE	VYHSNFKPL	EWT	1086.26	11.747	23.32 %
9mer_H2_Db	328	DQQ	MAEKVGDYM	ENH	1025.2	11.231	22.30 %
9mer_H2_Db	524	YMK	LVCRKSDNM	RVL	1047.25	10.643	21.13 %
9mer_H2_Db	514	TVA	HREDNVCYM	KLV	1148.28	10.591	21.03 %
9mer_H2_Db	444	LTP	VAIQAGRYL	ARR	972.16	10.381	20.61 %
9mer_H2_Db	272	AVE	YGITSDDLF	SLP	1012.09	9.69	19.24 %
10mer_H2_Db	464	TEL	TDYSNVATTV	FTP	1052.09	23.99	40.76 %
10mer_H2_Db	503	VYH	SNFKPLEWTV	AHR	1179.37	19.929	33.86 %
10mer_H2_Db	98	DEL	AGIVNESKYD	YDL	1077.16	15.442	26.24 %
10mer_H2_Db	568	DRT	IGIHPTCSET	FTT	1039.17	14.934	25.37 %
10mer_H2_Db	215	YKV	ALRDNQVTYL	NAK	1174.32	14.69	24.96 %
10mer_H2_Db	587	TKK	SGVSPIVSGC	UG	887.02	13.676	23.24 %
10mer_H2_Db	257	ILA	TGERPKYPEI	PGA	1171.33	13.328	22.64 %
10mer_H2_Db	423	DEQ	TTVSNVYAIG	DIN	1006.11	12.481	21.21 %
11mer_H2_Db	338	YME	NHGVKFAKLCV	PDE	1197.45	21.22	26.69 %
11mer_H2_Db	98	DEL	AGIVNESKYDY	DLI	1240.34	20.391	25.65 %
11mer_H2_Db	527	LVC	RKSDNMRVLGL	HVL	1270.51	13.574	17.08 %
11mer_H2_Db	205	QSH	IGSLNWGYKVA	LRD	1166.37	13.026	16.39 %
11mer_H2_Db	423	DEQ	TTVSNVYAIGD	INA	1121.2	12.765	16.06 %
11mer_H2_Db	474	TTV	FTPLEYGACGL	SEE	1152.34	11.753	14.78 %
11mer_H2_Db	358	LKV	VDTENNKPGLL	LVK	1181.3	10.68	13.43 %

Table 1: PSSM based prediction of MHC ligands, from whose C-terminal end are proteosomal cleavage sites.

MHC ALLELE	Rank	Sequence	Residue No.	Peptide
I-Ab	1	VATTVFTPL	518	1.126
I-Ab	2	RYLARRLFA	499	1.023
I-Ab	3	PTCSETFTT	621	0.996
I-Ab	4	SLPYFPGKT	330	0.991
I-Ad	1	QAGLLSHAL	216	0.924
I-Ad	2	GGSGGLAAG	164	0.765
I-Ad	3	GASYVALEC	342	0.724
I-Ad	4	GACGLSEED	529	0.709
I-Ag7	1	GIGAAKAFT	1	1.920
I-Ag7	2	GKEAAKYGA	172	1.916
I-Ag7	3	GGLAAGKEA	167	1.740
I-Ag7	4	VIFAVGREP	436	1.739
RT1.B	1	TTVFTPLEY	520	1.117
RT1.B	2	ETFTTLHVT	625	1.028
RT1.B	3	ATKADFDRT	608	0.927
RT1.B	4	TCSETFTTL	622	0.834

Table 2: SVM based prediction of promiscuous MHC class II binding peptides from antigen Protein.

Conclusion

Thioredoxin glutathione reductase of *Schistosoma mansoni* peptide nonamers are from a set of aligned peptides known to bind to a given MHC molecule as the predictor of MHC peptide binding. MHCII molecules bind peptides in similar yet different modes and alignments of MHCII ligands were obtained to be consistent with the binding mode of the peptides to their MHC class, this means the increase in affinity of

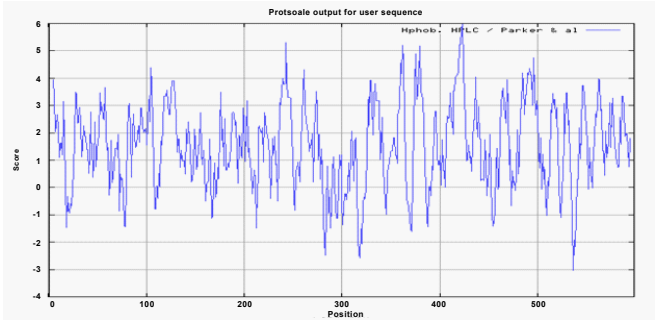

Figure 1: Antigenicity plot of antigen protein by Welling, et al. scale.

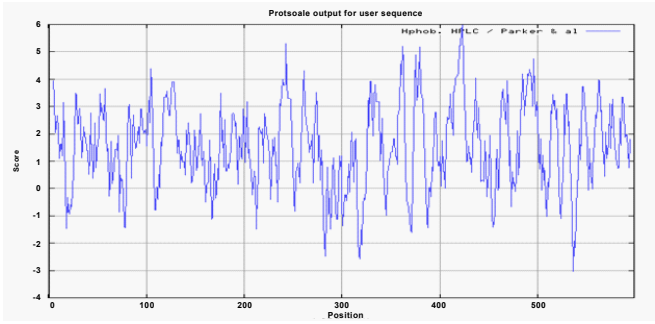

Figure 2: Antigenicity plot of antigen protein by HPLC / Parker, et al. scale.

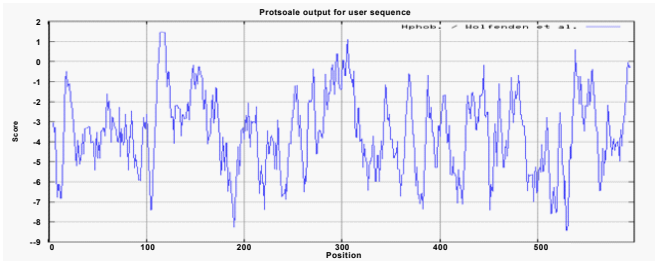

Figure 3: Hydrophobicity plot of antigen protein by Wolfenden, et al. scale.

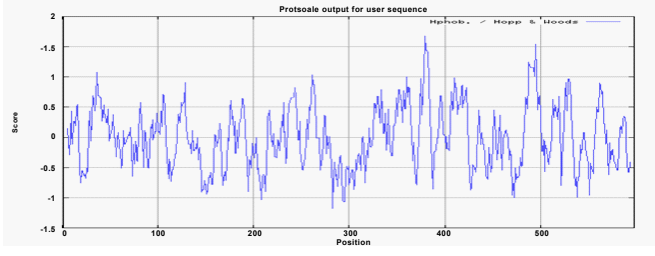

Figure 4: Hydrophobicity plot of antigen protein by Hopp & Woods scale.

MHC binding peptides may result in enhancement of immunogenicity of thioredoxin glutathione reductase. These predicted of thioredoxin glutathione reductase antigenic peptides to MHC class molecules are important in vaccine development from *Schistosoma mansoni*.

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