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Computational analysis of proteome of H5N1 avian influenza virus to define T cell epitopes with vaccine potential

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Abstract

The existing vaccines against influenza are based on the generation of neutralizing antibody primarily directed against surface proteins—hemagglutinin and neuraminidase. In this work, we have computationally defined conserved T cell epitopes of proteins of influenza virus H5N1 to help in the design of a vaccine with haplotype specificity for a target population. The peptides from the proteome of H5N1 virus which are predicted to bind to different HLAs, do not show similarity with peptides of human proteome and are also identified to be generated by proteolytic cleavage. These peptides could be made use of in the design of either a DNA vaccine or a subunit vaccine against influenza.
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1. Introduction

It has been difficult to develop a vaccine for influenza A virus that provides long lasting immunity. This is due to the antigenic drift of the virus where the circulating strain in an infectious cycle is different from the previously circulating strain [1,2]. Protection against influenza infection is conferred by neutralizing antibody for the two surface proteins, namely the hemagglutinin (HA) and the neuraminidase (NA) [3]. Apart from the antigenic drift, the appearance of reassortant virus carrying different H and N types pose serious problems by generating new virus strains [4,5]. The zoonotic influenza strains such as influenza A: H5N1, H9N2, H6N1, etc. cross species barriers and infect a cross-section of birds, humans and other mammals [6]. The vaccines currently in use against influenza comprise of formalin inactivated virus strains which are grown in embryonated eggs [7–9]; reassortant virus containing HA and NA of seasonal virus and other six genes of a master strain A/PR/8/34, and a cold adapted attenuated reassortant influenza vaccine that also contains HA and NA of recently circulating strain and other six proteins of cold adapted master strain [10]. The logistics of preparation of the vaccine is daunting and cost intensive. For these reasons, many investigators have often tried to look at the possibility of generating a universal vaccine useful against more than one influenza strain [11,12].

The preparation of a universal vaccine against influenza needs some basic considerations about the working of the influenza vaccine. Hemagglutinin protein is responsible for attachment of the virus to the sialic acid α-2,3 or α-2,6 galactose sugar receptor on the avian or human host cell surface [13]. It is reasonable to presume that influenza vaccines do not generate antibodies against the receptor binding region of the protein as this region is not subjected to much antigenic drift which would seriously compromise the infectivity of the virus. In fact, mutation in this region has resulted in change in sugar specificity leading to change of host specificity, and loosing infectivity for the original host species [13]. Antibodies directed against this region therefore are likely to provide

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protection against the influenza strains irrespective of their antigenic nature. Thus, one could assume that hemagglutinin receptor binding region is not immunologically dominant, and on vaccination the antibodies are made against neighboring immunodominant epitopes which sterically hinder receptor–hemagglutinin interactions. The other proteins of the virus are less subject to antigenic drift and possess many conserved epitopes. However, antibodies generated against these regions do not contribute to protective immunity, since they are made against internal proteins which are not surface exposed.

T cell immunity has been implicated in rapid clearance of influenza virus [1]. This means that the individual with good T cell response would suffer from milder form of the disease, get cured sooner, which is reflected in decreased fatality and less spread of the virus in population. Therefore, a vaccine generating robust T cell immunity against influenza needs serious attention. Good T cell immunity along with antibody response focused on receptor binding region of the hemagglutinin protein and enzymatic active site of neuraminidase, would meet the needs of a universal vaccine. Especially the internal proteins contain many conserved peptides which are potential T cell antigens and hence need serious consideration as T cell focused vaccine candidates.

In this communication, we have computationally analyzed the proteome of H5N1 influenza A subtype (A/Thailand/4(SP-528)/2004) [NCBI] and some of its variants to identify putative epitopes for the formulation of a recombinant chimeric vaccine for T cell immunity. This vaccine should cover the HLA haplotype of the target population, be effective against a wider spectrum of influenza A strains and not have any self-reactive epitopes and generate good immune memory response. The pathways for such an approach have been depicted in Fig. 1. A variety of computational tools are now available for prediction of T and B cell epitopes [14]. We have analyzed overlapping nonameric peptides of all the proteins of H5N1 influenza virus for binding to human HLA class I molecules by BIMAS [15], SYFPEITHI [16] and RANKPEP [17] algorithms, and for binding to class II alleles by PROPRED [18] and RANKPEP [19] computational HLA binding algorithms to select peptides for use in a polyepitope construct to develop a robust T cell vaccine. The peptides generated by these methods were also cross-checked for binding with respective HLA by PROPRED-I [20], ABCpred [21] and ANN/SMM tools available in IEDB [22].

We have modeled these peptides on corresponding HLA to validate the binding prediction. We have identified a number of peptides from each protein which bind to both class I and class II HLA by multiple analytical tools; these peptides are predicted to form stable complexes through molecular modeling and do not contain any human peptide of at least contiguous five amino acids or longer. These peptides can be used in a polyepitope construct to develop a robust T cell vaccine.

2. Methods

2.1. Virus and proteins

Hemagglutinin (AAV34704.1), neuraminidase (AAV32637), polymerase (AAS66086.1), nucleocapsid protein (AAS89187.2), matrix protein (AAS89185.2 M1 and AAS89186.2 M2), nonstructural protein (AAS89188 NS1 and AAS89189 NS2), polymerase basic proteins 1 and 2 (AAS89191.2 PB1 and AAS89190.2) and a cleavage protein, serine protease (NP_035775.1) are the proteins of H5N1 2004 Thailand strain available in the NCBI protein database, and have been used for this analysis. The five hemagglutinin variants of H5N1 (AAV34704.1) strain (AAS65615.2, AAT84153.1, AAS89004.2, AAV32636.1 and AAS65618.1) were taken from the NCBI database and were compared to identify antigenic drift in T cell epitope.

2.2. Predictions of MHC class I binding epitopes

All the eight proteins of the avian influenza A type of H5N1 Thailand strain 2004, namely hemagglutinin (HA), neuraminidase (NA), matrix protein 1 & 2 (M), nucleocapsid protein (NC), nonstructural protein 1& 2 (NS), polymerase basic protein 1 (PB1), polymerase basic protein 2 (PB2), polymerase (PA) and a cleavage protein protease were analyzed for the cytotoxic T lymphocyte (CTL) epitope using several algorithms. BIMAS [15] (http://bimas.dcrt.nih.gov/molbio/hla_bind) was used to analyze binding of all overlapping peptides to 33 alleles. This tool helped to identify those peptides in all the eight proteins and binds to the HLA molecules with a good binding affinity. The binding affinity ($T_{(1/2)}$ value) is based on the half-time of dissociation of the β2 microglobulin from HLA. A cutoff $T_{(1/2)}$ value of $\geq$100 was chosen for peptide selection. SYFPEITHI [16] and RANKPEP [17] are the two other algorithms which predict binding of nonameric peptides to 14 and 72 MHC class I HLA alleles, respectively. The optimal values for SYFPEITHI score of $\geq$15 and RANKPEP score at a threshold score of top 2% were chosen. The peptides which showed binding by all the three analytical procedures were selected. The selected peptides were further analyzed for binding to the identified HLA by PROPRED-I [20] and ANN/SMM tools of IEDB [22].

2.3. Prediction of MHC class II binding epitopes

The analysis for class II HLA binding was used to predict the binding affinity for those peptides which have shown class I HLA binding by use of PROPRED [18] and RANKPEP [19] algorithms of 51 and 49 MHC class II alleles, respectively. About 80% of MHC II restricted epitopes are found among the ∼5% top scoring peptides by PROPRED [18]. The threshold percent taken in this analysis was 2% to select high affinity peptides for RANKPEP [19].

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