International Journal of Bioinformatics and Biological Science: v.1 n.1 p.55-61. March, 2013

Computational epitope prediction and docking studies of glycoprotein-G in Nipah virus

Pramod Kumar Yadav[1*] and Mudit Mishra[2]

[1]Deptartment of Computational Biology & Bioinformatics, JSBB, SHIATS University, Allahabad-211007 (U.P.), India
[2]School of Bio Sciences and Technology, VIT University, Vellore-632014 (TN), India

[*]Corresponding Author: Pramod Kumar Yadav pramod.yadav@shiats.edu.in

Received: 24 December 2012; Accepted: 03 January 2013

ABSTRACT

Nipah viruses are highly pathogenic paramyxoviruses that have recently emerged from flying foxes or bats and horses to cause serious disease outbreaks in humans and livestock in many parts of the world. Their unique genetic constitution, high virulence and wide host range set them apart from other paramyxoviruses and they are designated as Biosafety level 4 pathogens. Many of the viruses are becoming resistant to some antiviral drugs e.g. Admantanes. Therefore, it is necessary to look for an alternative approach to combat the antiviral resistance. Nipah virus contains two membrane glycoproteins: the G glycoprotein, which is required for cell attachment, and the F glycoprotein, which is required for the fusion of the viral and host -cell membranes. The glycoprotein G plays an important role in the immunogenecity in the host cell. In the present work, *in silico* epitope prediction for glycoprotein-G in Nipah virus was carried out using variety of online tools. For B-cell epitope prediction, BCPREDS server and for the T-cell (MHC-I & MHC-II), IEDB analysis tool was used. In order to perform the docking study, top ranked predicted epitopes for the MHC class-I and MHC class-II were modeled using the Hhpred server. Subsequently, the predicted epitopes for the MHC-I and MHC-II were docked with their respective receptor using the PatchDock server. The lower energy score reveals higher binding affinity of predicted epitopes toward the receptor. It was found that the epitopes 'QTEGVSNLV' and 'LMMTRLAV' were showing highest binding affinity for the MHC-I and the epitopes 'SRPGQSQCPRFNTCP' and 'GQSQCPRFNTCPEIC' were showing highest binding affinity for the MHC-II. For the B-cell, epitope 'TNVWTPPNPNTVYHCSAVYN' was highest ranked epitope. These predicted epitopes might be promising vaccine candidates for Nipah virus.

Keywords: Epitope prediction, Glycoprotein-G, Modeling, Docking

BACKGROUND

Human Nipah virus infection was first recognized in a large outbreak of 276 reported cases in peninsular Malaysia and Singapore from September 1998 through May

1999(Paton *et al* ,1999). Most cases had contact with sick pigs(Parashar *et al* ,2000). The virus, a member of the recently designated genus *Henipavirus*, within the family *Paramyxoviridae*, was first isolated from a patient from Sungai Nipah village in Malaysia. The molecular basis of paramyxovirus virulence, host range and cell tropism is determined to a significant degree by the cell-attachment (G) and fusion (F) proteins, which determine host range and cell tropism by virtue of their roles in binding to cell receptors and fusing the virus and host-cell membranes; and by the products of the P gene, which modulate virulence by abrogating the cellular interferon (IFN) response. Recent studies on the structure and function of henipa virus proteins expressed from cloned genes have shown that the henipavirus G and F glycoproteins and the P protein also influence host range, cell tropism and virulence(Murray *et al* ,1995,Bossart *et al*,2001 and Eaton *et al* ,2006). Epitopes can be defined as parts of molecules that are specifically recognized by molecules of the immune system. The objective of the present work was *in silico* epitope prediction and docking studies for glycoprotein-G and in Nipah virus using variety of bioinformatics tools.

MATERIALS AND METHODS

The protein sequence of glycoprotein-G of Nipah virus was retrieved from the Uniprotkb databases at the Expasy site (Accession No. Q9IH62) (http://www.uniprot.org). For the prediction of B-cell epitopes, the protein sequence of glycoprotein-G was submitted to BCPREDS Server (http://ailab.cs.iastate.edu/bcpreds/)(Chen *et al* ,2007) This server is used for identification and characterization of B-cell epitopes which allows users to choose the method for predicting B-cell epitopes among several developed prediction methods. For the T-cell epitope prediction, IEDB analysis tool was used (http://tools.immuneepitope.org). This server covers a broad range of tools facilitating the prediction of new B- and T-cell epitopes in proteins of interest, and tools for the analysis of epitope sets collected from within the IEDB, or submitted by the user. For MHC class-I the epitopes were predicted for the alleles HLA-A*0101 and HLA-A* 0201 respectively. The epitopes were also predicted for MHC class-II (alleles HLA-DRBI 0101 & HLA-DRBI 0301). All the predicted epitopes were obtained in the form of small peptide sequences which were ranked according to their consensus percentile.

In order to perform the epitope-receptor docking, the 3D structure of predicted epitopes and MHC-I & MHC-II receptors were required. The 3D structures of the receptor for MHC Class I (PDB ID: 2X40) and MHC Class II (PDB ID: 1DLH) were retrieved from PDB databases (www.rcsb.org/pdb). The 3D structure prediction of all the MHC-I and MHC-II predicted epitopes were carried out by using the HHPred server (http://toolkit.tuebingen.mpg.de/hhpred). This is a free protein function and structure prediction server based on the HHsearch method. HHpred allows building a homology model using the Modeller program(Biegert *et al* ,2006,and Khan *et al* ,2011) The protein-protein docking of MHC receptor and predicted epitopes were carried out using the PatchDock server (http://bioinfo3d.cs.tau.ac.il/PatchDock). PatchDock is a geometry-based molecular

docking algorithm which is aimed at finding docking transformations that yield good molecular shape complementarity(Duhovny *et al*,2002) The top ranked predicted epitopes for MHC class-I were docked with MHC class-I receptor. Subsequently, top ranked predicted epitopes for MHC class-II were also docked with MHC class-II receptor. The epitope-receptor docked complexes were further refined using the FireDock program (http://bioinfo3d.cs.tau.ac.il/FireDock/). *FireDock* is an efficient method for refinement and re-scoring of rigid-body protein-protein docking solutions. Finally the docked complexes were saved, and based on their energy scores (KJ/mole) a comparative analysis was carried out.

RESULTS AND DISCUSSION

Result of B -cell epitope binding peptide prediction

Table 1 show the predicted B-cell epitopes which were predicted using the BCPREDS server. All the predicted epitopes were ranked according to their respective scores. Higher score of the peptides reveals the higher probability to be most suitable epitope for the human B-cell.

Table 1: B- cell predicted epitopes

S. No.	Rank	Position	Epitope	Score
1.	1	268	TNVWTPPNPNTVYHCSAVYN	0.999
2.	2	345	YDKVMPYGPSGIKQGDTLYF	0.993
3.	3	161	SCPNPLPFREYRPQTEGVSN	0.990
4.	4	315	MMTRLAVKPKSNGGGYNQHQ	0.982
5.	5	134	STASINENVNEKCKFTLPPL	0.980
6.	5	11	ENTTSDKGKIPSKVIKSYYG	0.980
7.	6	476	VVNWRNNTVISRPGQSQCPR	0.970
8.	7	62	IIVMNIMIIQNYTRSTDNQA	0.933
9.	8	294	LCAVSTVGDPILNSTYWSGS	0.912
10.	9	98	ADKIGTEIGPKVSLIDTSST	0.857

Result of MHC Class-I binding epitope prediction

Tables 2-3 show the predicted T-cell MHC Class-I, epitopes for alleles HLA-A*0101 and HLA-A*0201 respectively. These small peptides (epitopes) were predicted by the IEDB analysis tool and ranked according to their consensus percentile rank.

Table 2: MHC I (HLA-A*0101) Binding Peptide Prediction

Ranks	Sequence	Pep. length	At position	Consensus percentile rank
1	AMDEGYFAY	9	1:223-231	0.15
2	LSDGENPKV	9	1:418-426	0.65
3	QTEGVSNLV	9	1:174-182	0.70
4	CSAVYNNEF	9	1:282-290	0.75

Table 3: MHC I (HLA-A*0201) Binding Peptide Prediction

Ranks	Sequence	Pep. length	At position	Consensus percentile rank
1	LMMTRLAV	8	1:314-321	0.20
2	KFGDVLTV	8	1:465-472	0.30
3	VLCAVSTV	8	1:293-300	0.50
4	SMGIRPNS	8	1:398-405	0.80

Result of MHC Class-II binding epitope Prediction

Tables 4-5 show the small peptides (epitopes) for MHC class-II predicted by IEDB analysis tool which were ranked according to their consensus percentile rank.

Table 4: MHC II (HLA-DRBI 0101) Binding Peptide Prediction

Ranks	Sequence	Pep. length	At position	Consensus percentile rank
1	SRPGQSQCPRFNTCP	15	1:486-500	94.86
2	RPGQSQCPRFNTCPE	15	1:487-501	94.92
3	PGQSQCPRFNTCPEI	15	1:488-502	96.55
4	GQSQCPRFNTCPEIC	15	1:489-503	96.98

Table 5: MHC II (HLA-DRBI 0301) Binding Peptide Prediction

Ranks	Sequence	Pep. length	At position	Consensus percentile rank
1	SRPGQSQCPRFNTCP	15	1:486-500	94.86
2	RPGQSQCPRFNTCPE	15	1:487-501	94.92
3	PGQSQCPRFNTCPEI	15	1:488-502	96.55
4	GQSQCPRFNTCPEIC	15	1:489-503	96.98

Docking results of MHC-I epitopes

Top ranked predicted epitopes for different alleles of MHC class-I were docked with human MHC-I receptor using the PatchDock server. The results have been shown in the Tables 6-7.

Table 6: Energy score of MHC I predicted epitopes (HLA-A*0101)

Epitope	Receptor	Global Energy (KJ/Mole)	Attractive VdW	Repulsive VdW	ACE	HB
1979062.pdb	2X4O.pdb	-50.80	-30.32	10.16	-1.38	-1.34
5910907.pdb	2X4O.pdb	-55.68	-32.40	14.86	-6.75	-1.09
1483671.pdb	2X4O.pdb	-64.33	-37.22	23.10	-0.86	-3.54

9300098.pdb	2X4O.pdb	-67.73	-41.86	14.93	-2.69	-1.88

Table 7: Energy score of MHC I predicted epitopes (HLA-A*0201)

Epitope	Receptor	Global Energy (KJ/Mole)	Attractive VdW	Repulsive VdW	ACE	HB
6621841.pdb	2X4O.pdb	-65.31	-42.60	28.21	-10.19	-2.75
3405542.pdb	2X4O.pdb	-65.93	-40.49	31.48	-3.80	-6.41
1644675.pdb	2X4O.pdb	-61.80	-36.41	15.81	-3.81	-0.40
6050153.pdb	2X4O.pdb	-59.05	-29.24	16.90	-16.03	-3.05

Docking results of MHC-II epitopes

Top ranked MHC class-II predicted epitopes were also docked with human MHC-II receptor. The results have been shown in the Tables 8-9.

Table 8: Energy score of MHC-II predicted epitopes (HLA-DRBI 0101)

Epitope	Receptor	Global Energy (KJ/Mole)	Attractive VdW	Repulsive VdW	ACE	HB
5659836.pdb	1DLH.pdb	-74.58	-26.39	8.68	-6.97	-0.97
9470833.pdb	1DLH.pdb	-75.67	-42.84	25.05	-12.85	-2.31
7779538.pdb	1DLH.pdb	-72.55	-40.30	23.07	-4.88	-4.23
3808639.pdb	1DLH.pdb	-75.95	-35.79	10.00	-9.39	-2.98

Table 9: Energy score of MHC-II predicted epitopes (HLA-DRBI 0301)

Epitope	Receptor	Global Energy (KJ/Mole)	Attractive VdW	Repulsive VdW	ACE	HB
7009956.pdb	1DLH.pdb	-74.58	-26.39	8.68	-6.97	-0.97
7864729.pdb	1DLH.pdb	-51.82	-31.32	29.31	-8.74	-4.14
9278511.pdb	1DLH.pdb	-74.17	-41.49	7.45	-4.68	-3.67
7044257.pdb	1DLH.pdb	-63.74	-35.52	9.90	-0.21	-1.56

Abreviations: ACE- The contribution of the atomic contact energy (ACE) to the global binding energy HB- The contribution of the hydrogen bonds to the global binding energy

The top ranked predicted MHC class-I and MHC class-II epitopes were docked with their respective receptors. The epitope-receptor complexes were visualized by the PyMol tool which has been depicted in Figure 1.

Nipah virus contains two membrane glycoproteins: the G glycoprotein, which is required for cell attachment, and the F glycoprotein, which is required for the fusion of the viral and host -cell membranes. The glycoprotein G plays an important role in the immunogenecity in the host cell(Bossart *et al*,2001).The present work was carried out to predict the antigenic epitopes for glycoprotein-G in Nipah virus. The epitopes for B-cell & T-cell were predicted respectively using the variety of tools.

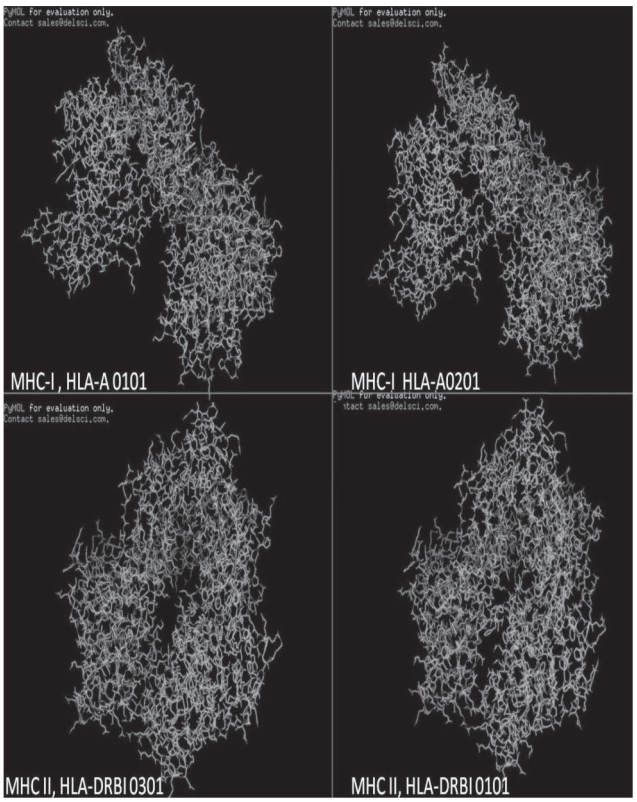

Figure 1: The 3D structures of the docked complexes of epitopes

Earlier *in silico* epitope prediction were successfully carried out for different organisms(Yadav and Rana ,2011, Ingale 2010 and Yadav *et al* ,2011). For the B-cell epitope prediction BCPREDS server was used, which predicted 14 epitopes and rank has been given the basis of score. The higher score for the predicted B-cell epitope reveals most suitable epitope for the human B-cell. According to their scores, top 10 B-cell predicted epitopes have been shown in Table 1. The epitopes for T-cell were predicted using the IEDB Analysis tool. The epitopes predicted for MHC Class-I and MHC Class–II have been shown in the Table 2-5. The T-cell epitope prediction was carried out for the human alleles HLA-A*0101 and HLA-A*0201 of MHC class-I and HLA-DRBI 0301 and HLA-DRBI 0301 of MHC Class-II. The alleles are commonly expressed in immune responses against the viral infections. On the basis of their consensus percentile rank, top four predicted epitopes for each allele were chosen. For MHC class I, low percentile is treated as good binders and for MHC class II, high percentile is treated as good binders. In order to perform the docking studies with their respective human T-cell receptors, three dimensional structures of predicted epitopes were required. The HHPred server was used for 3D structure prediction of top ranked epitopes (small peptides). This

server uses homology modeling method integrated with Modeller tool. After obtaining 3D structures of predicted epitopes, the protein-protein docking studies were performed using the PatchDock web server. The top ranked predicted epitopes for MHC class-I and MHC class-II were docked with human MHC class-I and MHC class-II receptor respectively. The Table 6-9 shows the energy score of epitope-receptor complexes. Low energy score reveals high binding affinity toward their respective receptors. Those predicted epitopes for B-cell and T-cell can be exploited for the vaccine design against the Nipah virus so that outbreaks caused by these viruses can be prevented effectively.

CONCLUSION

Based on computational epitope prediction and docking studies, it can be concluded that 'QTEGVSNLV' epitope (for the allele HLA-A*0101) and 'LMMTRLAV' epitope (for the allele HLA-A* 0201) were having the least energy score for MHC-I receptor which reveals highest binding affinity for MHC-I. For the MHC-II receptors, it was found that 'SRPGQSQCPRFNTCP' epitope (for the allele HLA-DRBI 0101) and 'GQSQCPRFNTCPEIC' epitope (for the allele , HLA-DRBI 0301) were having the least energy score which reveals highest binding affinity for MHC-II receptor. The small peptides 'TNVWTPPNPNTVYHCSAVYN' and 'YDKVMPYGPSGIKQGDTLYF' were most probable epitopes for the B-cell. In future, these predicted epitopes can be synthesized in wet laboratory which might be promising candidates for the vaccine design against Nipah virus.

REFERENCES

Biegert, A., Mayer, C., Remmert, M., Söding, J. and Lupas, A. 2006. The MPI Toolkit for protein sequence analysis *Nucleic Acids Res.* **34**, W335-339.

Bossart, K.N., Wang, L.F., Eaton, B.T. and Broder, C.C. 2001. Functional expression and membrane fusion tropism of the envelope glycoproteins of Hendra virus. *Journal of Virology,* **290:**121-135.

Chen, J., Liu, H., Yang, J., Chou, K. 2007. Prediction of linear B-cell epitopes using amino acid pair antigenicity scale. Amino Acids **33**:423-428.

Duhovny, D., Nussinov, R. and Wolfson, H.J. 2002. Efficient Unbound Docking of Rigid Molecules. In Gusfield et al., Ed. Proceedings of the 2'nd Workshop on Algorithms in Bioinformatics (WABI) Rome, Italy, *Springer Verlag,* **2452**:185-200.

Eaton, B.T., Broder, C.C., Middleton, Deborah and Wang, L.F. 2006. Hendra and Nipah viruses: different and dangerous, *Nature Reviews Micrbiology,* **4**: 25.

Ingale, A.G. 2010. *In Silico* Homology Modeling and Epitope Prediction of Nucleocapsid Protein region from Japanese Encephalitis Virus, *Journal of Computer Science & Systems Biology*, **3(2):** 053-058.

Khan, A.U., Baig, M.H. and Wadhwa, G. 2011. Molecular docking analysis of new generation cephalosporins interactions with recently known SHV-variants. *Bioinformation,* **22**:331-5.

Murray, K.P., Selleck, P., Hooper, A., Hyatt, A., Gould, L., Gleeson, H., Westbury, L., Hiley, L., Selvey, B. and Rodwell. 1995. A morbillivirus that caused fatal disease in horses and humans. *Science*, **268**: 94-97.

Parashar, U.D., Sunn, L.M. and Ong, F. 2000. Case-control study of risk factors for human

infection with a new zoonotic paramyxovirus, Nipah virus, during a 1998-1999 outbreak of severe encephalitis in Malaysia. *The Journal of Infectious Diseases*, **181(5)**: 1755–1759.

Paton, N.I., Leo, Y.S. and Zaki, S.R. 1999. Outbreak of Nipah-virus infection among abattoir workers in Singapore. *Lancet*, **354(9186)**:1253–1256.

Peters, B., Sidney, J., Bourne, P., Bui, H.H., Buus, S., Doh, G., Fleri, W., Kronenberg, M., Kubo, R. and Lund, O. 2005. The immune epitope database and analysis resource: from vision to blueprint. *PLoS Biology*, **3**:e91.

Yadav, P.K. and Rana, J. 2011.Computer aided epitope prediction for glycoprotein-B in human cytomegalovirus. *Elixir Bio. Phys.*, **39**:5021-5025.

Yadav, P.K., Singh, R., Jain, P.A., Singh, S., Gautam, B. and Farmer, R. 2011. *In silico* epitope prediction for Glycoprotein D in Human Herpes Simplex Virus-1, *International Journal of Pharmaceutical Sciences Review and Research*, **7(2)**:148-152.