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Interaction between a Peptide and White Spot Syndrome Virus VP28 Envelope Protein

Xiaofeng Ji, Yuan Zheng, Jun Sheng*

Yellow Sea Fisheries Research Institute, Chinese Academy of Fishery Sciences, Qingdao, China
Email: *shengjun@ysfri.ac.cn

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Abstract

White spot syndrome virus (WSSV) is one of the most important pathogens that endanger the global shrimp aquaculture. Studies have confirmed that in the early stage of infection, VP28, the main envelope protein of WSSV, is used as a viral adhesion protein to bind PcRab7 of *Penaeus chinensis*, helping virus enter the host cells, resulting in shrimp infection. Hence, inhibition of envelope protein VP28 would be a novel way to deal with the infection. Peptide 2E6 was confirmed to have a high specificity and blocked virus infection. However, the mechanism by which it combines with VP28 is not clear. Clarifying the binding mechanism between peptides and VP28 is of great significance for further optimization and screening of antiviral peptides. In this research, the MD simulation and binding free energy analysis were implemented to validate and capture intermolecular interactions aims to clarify the blocking mechanism.

Keywords

White Spot Syndrome Virus, VP28

1. Introduction

White spot syndrome (WSSV) is a syndrome caused by white spot syndrome virus (WSSV). It is one of the most harmful pathogen of cultured shrimp worldwide [1]. It is an important aquatic animal infectious disease required to be reported by OIE. Since the outbreak of the disease in 1992, the disease caused a large area of death of prawn, and has still brought great economic losses to shrimp aquaculture. The prevention and control of white spot syndrome is of great significance to the healthy culture of prawn [2].

The genome size of WSSV is about 300 KB. It is predicted that WSSV encodes about 180 proteins, among which more than 50 proteins encoded by viruses are

identified as structural proteins [3]. Among these structural proteins, envelope protein is an important determinant of viral infection and pathogenicity [4], and is considered to be the first molecule directly contacting with the host [5] [6], so it plays a key role in cell targeting and host defense. VP28, the major envelope protein, has an important role in the infection process and is required for the attachment of the virus to shrimp cells and its complete internalization [7]. Results of immune-electron microscopy confirmed that VP28 was distributed on the outer surface of the virus [8]. During infection, VP28 serves as a viral binding protein binds to Rab7 protein in shrimp cells and mediates the fusion of virus envelope and host cell membrane, thus helping virus to enter host cells [7] [9], which plays a key role in the early stage of WSSV infection [8]. Therefore, the envelope protein VP28 is an ideal target for screening antiviral drugs [10] In the screening of WSSV antiviral lead compounds, peptide ligands with anti WSSV activity were obtained through phage surface display using VP28 as the target [11] and antibody peptide ligand screening [12] [13] [14]. Especially, Yi *et al.* selected a phage-displayed peptide 2E6 can specifically bound to WSSV, it also had a high specificity and blocked virus infection, with the possible critical motif for virus inhibition being VAVNNSY. However, its interaction mechanism is unclear. It is not possible to further optimize the drug molecules. The designed compounds have complex structures and cannot be used as candidate drugs for further research against WSSV.

In this research, we determined the interaction interface and interaction sites of antivirus peptides 2E6 (AP) and the major envelope protein (VP28) of WSSV to clarify the inhibition mechanism. This study will also provide a new way for further screening and design of anti-disease drugs for aquatic animals.

2. Material and Methods

The crystal structure of the envelope protein VP28 of WSSV (PDB id: 2ED6, Chain A) has been used as the receptor in this study. Complex of VP28 and the peptide inhibitor (VP28-AP) was generated by using the online server of HPEPDOCK 2.0 (http://huanglab.phys.hust.edu.cn/hpepdock/) [15].

In this study, the MD simulations were undertaken by using the Amber16 package. The complex model VP28-AP were solvated in a 20 $Å^3$-sized cubic box of TIP3P water molecules, and the parameters for the amino acids and peptide were assigned using the AMBER-FF14SB force field. Sixteen Na ions were added to neutralize the system. The systems were minimized with the SANDER program using 2500 steps of the steepest descent algorithm followed by 5000 steps of the conjugated gradient algorithm. The calculation steps and parameter setup were the same as those in our previous work. Finally, the module of cpptraj in amber16 software package was used to analyze the resulting trajectories. For the complex system, binding energies were computed using the popular MMGBSA module of AMBER over the 10 ns trajectory after equilibrium and using a 2 ps frame separation interval.

3. Results and Discussion

The tertiary structure of VP28 was defined as the receptor and the peptide AP was defined as ligand. Then we upload the 3D structure and sequence to the online server of HPEPDOCK 2.0 and then we selected default values for all parameters. All the structures in the largest cluster were sorted according to the free energy, and the conformation with the lowest binding free energy was selected as the conformation of VP28-AP complex (Figure 1(a)) for further analysis. From the interaction map (Figure 1(b)) we can easily found that, the interaction interface of VP and AP mainly concentrated in the N-terminal of VP28. AP binds to VP28 through sites THR135, HIS195, ASN51, GLN138 and ASN154. These residues were speculated to be the key site affecting the binding of AP and VP28.

By using the complex structure of VP28-AP as the initial structure, 500 ns MD simulation were taken. During the whole simulation the backbone RMSD of the system showed a rapidly increases to 2.5 Å, then fluctuated around 2.5 Å (Figure 2), indicating the complex attained equilibration during MD simulation and the last 50 ns after equilibration was selected to calculate the binding energy. The results of MM-GBSA were summarized in Table 1. It can be found that polar solvation plays a positive role while no-polar solvation plays a negative role in the interaction of AP and VP28. At the same time, considering the contribution of different energy terms we can find that van der Waals, electrostatic and accessible surface area energy were all play negative roles except polar solvation energy.

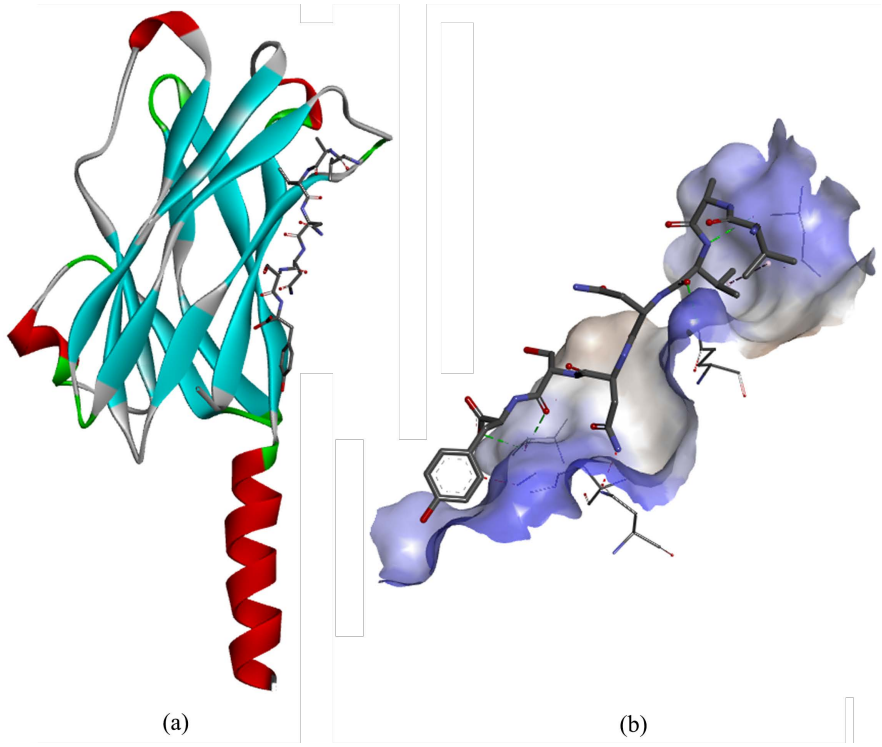

Figure 1. (a) The complex of VP28 and peptide AP Residues in VP28 were shown in cartoon stick and residues in AP were shown in stick. (b) The binding sites of VP28 and AP. The receptor surfaces were shown in hydrophobicity.

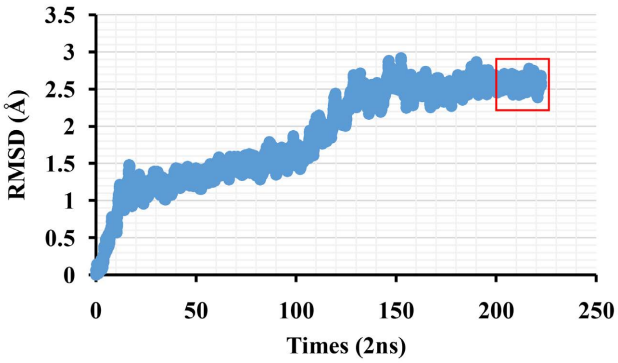

Figure 2. The RMSD for the complex of VP28-AP.

Table 1. Molecular mechanics. Generalized Born Surface Area (MM-GBSA) values (binding free energies) of VP28-AP complexes. Results are presented as average ± std. Err.

Energies (kcal/mol)		VP28-AP
G_{gas}	Electrostatic	−11.36 ± 0.41
	Van der Waals	−4.22 ± 0.46
G_{solv}	GB	15.25 ± 0.72
	SURF	−2.76 ± 0.36
Binding energy		−3.11 ± 1.55

4. Conclusion

Previous studies have shown that peptide 2E6 has antiviral effects on VP28, but its interaction mechanism is unclear. In this research, we implemented the MD simulation and binding free energy analysis to validate and capture intermolecular interactions aims to clarify the interaction mechanism between VP28 and antivirus peptide 2E6. The result showed that the interaction interface is in the N-terminal of VP28. AP binds to VP28 through sites THR135, HIS195, ASN51, GLN138 and ASN154. These residues were speculated to be the key site affecting the binding of AP and VP28. In order to develop potential antiviral drugs, it is necessary to understand the binding of "target proteins" to drugs, and the screening of specific antiviral peptides can provide a basis for the design and development of antiviral drugs. This design approach is common in the design of antiviral drugs, but there have been no relevant reports on the development of aquatic drugs. These results will contribute to a deep understanding of the interaction mechanism of antivirus peptide and WSSV and will also provide ideas for the discovery and optimization of lead compounds against WSSV.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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