Analysis of Global Ecosystem Ecology by Fragment Molecular Orbital (FMO) Method – Analyses of the interactions between virus hemagglutinins and their receptors –

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To understand the basis of global expansion of virus diseases, we analyzed the interaction between viral envelope protein and host receptor by using the Earth Simulator of JAMSTEC and fragment molecular orbital (FMO) method. We focused our attention to two virus groups, influenza viruses and morbilliviruses. Avian influenza viruses use sialic acid linked to galactose by an α2, 3 linkage (2-3 type), whilst human viruses use that by α2, 6 linkage (2-6 type), as the receptor. We examined the affinity of hemagglutinin (HA) of avian-origin H7N9 viruses, which have recently been reported to transmit to humans, to the receptors of humans and of birds. The FMO analysis showed that the HA protein of H7N9 has higher affinity to the human type of receptor, compared to low affinity of conventional avian H7N3 virus. These results agreed with the experimental data, and we have also elucidated the molecular mechanism underlying the binding affinities through comparative FMO analyses at residue level for the complexes between avian or human influenza virus HA and avian or human receptor.

Signaling lymphocyte activating molecule (SLAM) is a host receptor to which the morbillivirus HA protein binds. Using the crystal structure of the complex between measles virus (MV) HA and monkey SLAM, three dimensional (3D) structures of the complex of HA and the SLAMs of the other morbilliviruses and mammals were estimated by molecular dynamics calculations, respectively. FMO analysis showed that the binding affinities of MV-HA to the SLAMs of several mammals, such as human, monkey and seals, were estimated. They agreed with the infectivities of the viruses to these animals. However, those of the CDV-HA to SLAMs of several mammals were not well agreed. This was probably caused by low resolution of the 3D structure estimation of the HA and SLAM proteins.

The present study showed that FMO method is useful to estimate the interaction of the virus and its receptor, if their 3 D structures are available. To obtain better results, we need better 3D structure estimation method for the complexes of the virus HA and the receptor.

Keywords: Influenza virus, morbillivirus, receptor, fragment molecular orbital method, hemagglutinin, signaling lymphocyte activating molecule

1. Introduction

Recently pathogenic viruses are attracting much attention for human diseases and also for wild life diseases. Zoonotic viruses e.g. influenza virus, which infect not only humans but also wild animals, such as birds, are becoming more and more important for human health. In addition, the expansion of host range of viruses may cause a serious damage to the new host animals and to the ecosystems. Highly virulent avian influenza virus is now thought to be a potential threat to humans and poultry [1, 2]. In marine mammals, morbilliviruses cause mass mortalities in seals

and whales [3, 4]. One of the morbilliviruses, canine distemper virus (CDV), which has been thought to cause a severe disease, canine distemper, mostly in dogs, is now known to cause the disease also in seals and large cats [5].

The receptor molecules on the host cells play an essential role in viral attachment for invasion and determination of host tropism. The purpose of the present study is to simulate the interactions between the viruses and their receptors on the host animal cells by using fragment molecular orbiter (FMO) method and the Earth Simulator.

We focused our attention to two virus groups; influenza viruses and morbilliviruses. Humans and birds are major and natural hosts for influenza viruses, and the viruses use sialic acid as receptors to invade. Humans possess sialic acids linked to galactose by an α2, 6 linkage (2-6 type) on the epithelial cells of trachea, whilst birds possess those by an α2, 3 linkage (2-3 type) on the cells of intestine [6]. Human and avian viruses usually independently circulate in their natural hosts by using their specific receptors. However, unexpected transmissions of highly virulent avian influenza to humans have been reported [7]. Avian-origin influenza virus, the type H7N9 showed a high pathogenicity to humans [2]. In the present study, we simulated the interaction between the virus hemagglutinin (HA) of the avian-to-human H7N9 type and sialic acid receptors, in comparison with that of the avian H7N3 influenza viruses based on recently reported three-dimensional (3D) structures of the receptor-HA complexes [8, 9].

Signaling lymphocyte activating molecule (SLAM; CD150) is a host receptor for morbilliviruses [10]. SLAM is a member of SLAM family proteins (immunoglobulin superfamily), and its variable region (V) like domain provides an interface with morbilliviruses. To understand the high virus-host specificity of morbilliviruses, the interfaces of various animal SLAM sequences has been analyzed by 3D homology modelings based on the crystal structure of the other SLAM family proteins or of the complex between measles HA and monkey SLAM V region [11, 12, 13, 14]. In the present study, the interaction between HA protein of three morbillivirus species, MVs (L482R mutant and wild type), and CDV, and their host animal SLAMs, were examined by FMO method.

2. Materials and computational methods

2.1 Analysis of influenza virus-host receptor interaction

We employed X-ray crystal structures of complexes of HA protein (H7N3 or H7N9 type) and human or avian receptor [8, 9]. Their PDB codes are 4BSH (H7N3 and human receptor 6'SLN), 4BSI (H7N3 and avian receptor 3'SLN), 4KON (H7N9 and human receptor 6'SLNLN) and 4KOM (H7N9 and avian receptor 3'SLNLN). These H7N3 and H7N9 type HAs may be regarded as hemagglutinin proteins of avian and human infection type, respectively. Figure 1 illustrates the molecular structure of

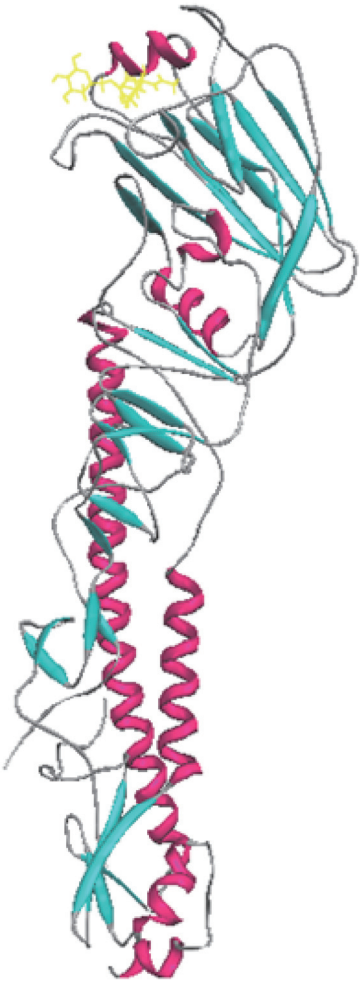

Fig. 1 X-ray crystal structure of the complex of A/Anhui/1/2013 (H7N9) HA and human receptor (PDB entry: 4KON). The receptor (sialosaccharide) part is denoted by yellow color.

4KON. Hydrogen atoms were added to these complexes by the MOE (Molecular Operating Environment) software (Chemical Computing Group Inc.), and their positions were optimized with the Amber99 force field.

The FMO calculations [15, 16, 17, 18, 19] with the software ABINIT-MP were performed for these complexes, where we employed the Hartree-Fock (HF) and the second-order Møller–Plesset (MP2) perturbation methods with the basis set of 6-31G. While the HF method is a mean-field type approximation, the MP2 perturbation method is employed for the description of electron correlations in the present study, where the latter is expected to take into account the dispersion (or van der Waals) interactions appropriately [19]. Thus, we can quantitatively evaluate the binding energy in terms of the present MP2 method.

2.2 Analysis of morbillivirus-host receptor (SLAM) interaction

Docking structures of morbillivirus hemagglutinin (MoV-HA) proteins and their receptors on animal cells (SLAMs) were constructed by homology modeling followed by molecular dynamics (MD) simulations. MoV-HA and SLAM-V (V region of SLAM) sequences retrieved from Protein Data Bank (PDB)

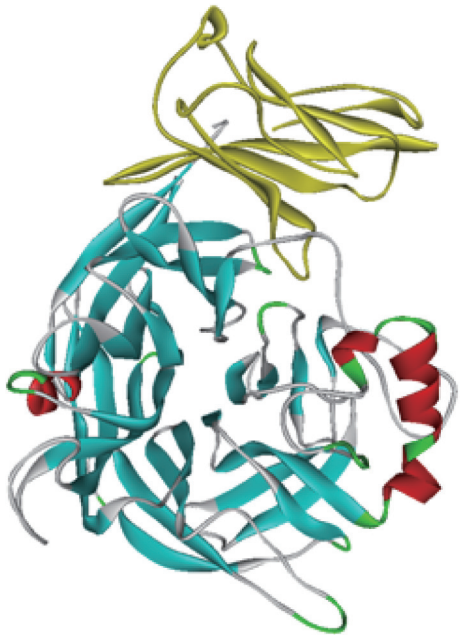

Fig. 2 The crystal structure of the measles virus hemagglutinin and its receptor protein the signaling lymphocyte activating molecule domain V from marmoset. The receptor is shown in yellow.

and GenBank were: measeles virus (MV-L482R, one point mutant Leu482Arg of MV) PDB: 3ALX, wild type measeles virus (MV-Wild) AB012948, canine distemper virus (CDV-HA) AF164967, human SLAM-V NM_003037, marmoset SLAM-V PDB: 3ALX, dog SLAM-V AF325357, seal SLAM-V AB428368 and mouse SLAM-V NM_013730. Some chimeric mouse SLAM-Vs, mouse/63h, mouse/60h/61h and mouse/60h/61h/63h, were developed by a point mutation tool in Discovery Studio (Accelrys), which had 1, 2 or 3 points of human type amino acid substitutions on the positions indicated in their names (delimited with slash symbol).

Crystal structure of the measles virus hemagglutinin (MV-L482R) - marmoset SLAM V domain (marSLAM-V) complex PDB: 3ALX reported by Hashiguchi et al. [14] was used for both homology modeling template and coarse docking template in the model building (Fig. 2). Homology modeling, docking and energy minimizations were done using Discovery Studio under the CHARM22 force field [20, 21]. Optimization of molecular interface between MoV and SLAMs were achieved by 3 steps of energy minimization. In the first step, amino acids on the interface within 5 Å from each other protein was fixed, and remaining part (outside of interface) was optimized until the RMS (RMS: root mean square) gradient value reached a value smaller than 0.001. Second step, the fixed part was inverted and minimization was done in the same condition. For the last step, whole system was optimized, and the resultant model was used for MD and FMO simulations.

MD simulations were conducted to obtain relaxed docking models in explicit water solvent, were performed using combination of VMD [22] and NAMD [23] software running on the JAMSTEC super computer system (SGI ICE X Linux cluster). The simulations were carried out for times of up to 900 ns at 300 K, with a minimum step time of 1 fs. The molecular complex model was solvated with explicit water in the minimum depth of 20 Å from protein surface. All calculations were carried out using an NVT ensemble (NVT: constant number of particles, constant volume and constant temperature). The periodic boundary condition and particle mesh Ewald method were enabled for the study. After the calculations, protein structures at 900 ns were sampled from trajectories.

To investigate the interactions between MoVs and SLAM-Vs in a quantitative way, FMO (FMO: fragment molecular orbital) calculations worked out by ABINIT-MP package were chosen because of its high accuracy and high computational efficiency. We performed the FMO calculations with second-order Møller-Plesset perturbation theory (MP2) and the 6-31G basis set. The input protein models were divided at individual amino acid residues as “fragment”. The IFIE (IFIE: inter-fragment interaction energy) between MoV-HA and SLAM-V calculated by FMO method was used for the comparison of infectious risk.

3. Results

3.1 Interaction between influenza virus and the receptor

Table 1 lists the interaction energies between H7N3 (A/Turkey/Italy/214845/2002) or H7N9 (A/Anhui/1/2013) type HA and parts (SIA1, GAL2, NAG3 and GAL4, where SIA, GAL and NAG refer to sialic acid, galactose and N-acetyl glucosamine, respectively) of avian or human receptor obtained by the FMO calculations. As observed in this table, the H7N9 influenza virus HA shows weaker attractive interactions with the avian receptor than the H7N3 influenza virus HA, but even the former still keeps a moderate binding to the avian receptor. The H7N9 influenza virus HA, (Anhui), which may be regarded as a mutant from H7N3 influenza virus HA, shows a much stronger binding to the human receptor than to the avian receptor. The former binding is stronger than that between the H7N3 influenza virus HA and the avian or human receptor.

We have then investigated the molecular mechanism for these binding properties at the residue level and revealed the importance of structural changes of the HA-receptor complexes caused by the mutations (indirect effect) as well as the importance of the modification of interactions between the mutated residues and the receptors (direct effect). We can thus perform structure-based theoretical analyses of the binding affinity of HA-receptor complex in terms of accurate quantum-chemical calculations, which would provide useful information for the prediction of possible interspecies transmission associated with influenza pandemic and the development of influenza vaccines against target HA proteins with forthcoming mutations. More details concerning the molecular level studies will be reported elsewhere.

3.2 Morbillivirus-SLAM interaction

To examine the suitability of the calculation method of the morbillivirus-SLAM interaction, the MV and marmoset SLAM-V complex that consist of 419 and 109 amino acids respectively, was calculated by the FMO2-MP2/6-31G on 128 processors of the Earth Simulator 2. The total number of amino acid, fragment, electron and basis set were 528, 522, 31364 and 45438, respectively. The difference between total amino acids number and fragment number was derived from 6 disulfide links (cysteine-cysteine) in the complex model. The job took about 70 minutes.

We examined 26 kinds of data set in combinations of 3 types of MoV-HA (MV-L482R, MV-Wild, CDV), 8 types of SLAMs (marmoset, human, dog, spotted seal, mouse, chimera mouse/60h/61h, chimera mouse/60h/61h/63h, chimera mouse/63h) and 2 optimizing conditions (energy minimized model and relaxed model in water) by the FMO calculations. The results are shown in Table 2. FMO analysis showed that the interaction energies between MV-L482R and SLAMs of marmoset, dog and spotted seal, were reasonable in the order of the sensitivities of the animals to the MV. The same results were observed in the case of MV-Wild. However, the interaction energies of the CDV-H to SLAMs were not well estimated. The problem was probably caused by the accuracy of complex models depending on the quality of homology modeling and molecular dynamics simulations. We cannot go into great depth in considering them this time, but expect that further refinement will take place in the future.

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Table 1 Interaction energies (in units of kcal/mol) between HAs of H7N3 or H7N9 and each part of saccharide receptors. (a) Avian receptor. (b) Human receptor. Sums of each contribution are also shown.

(a)

	SIA1	GAL2	NAG3	GAL4	Total (SIA1+GAL2+NAG3)	Total+GAL4
H7N3 (avian)	-188.8	-3.8	2.0		-190.6	
H7N9 (human)	-186.3	0.6	6.4	-1.8	-179.3	-181.1
⊿IFIE	-2.5	-4.4	-4.4		-11.3	

(b)

	SIA1	GAL2	Total IFIE
H7N3 (avian)	-183.6	-3.0	-186.6
H7N9 (human)	-204.2	0.9	-203.3
⊿IFIE	20.6	-3.9	16.7

Table 2 Interaction energies between morbillivirus hemagglutinins and mammalian signaling lymphocyte activating molecules (SLAMs). GenBank and Protein Databank accession numbers for viruses and SLAMs are shown in parentheses. Symbols for the infectiveness column: +, infectable; -, not infectable.

Virus	SLAM	Infectiveness	IFIE (kcal/mol)	
			Optimized	Relaxed
MV-L482R (PDB: 3ALX)	Marmoset (PDB: 3ALX)	+	-861	-773
	Human (NM_003037)	+	-849	-606
	Dog (AF325357)	-	-840	-666
	Spotted seal (AB428368)	-	-779	-497
MV-Wild (AB012948)	Marmoset (PDB: 3ALX)	+	-932	-644
	Human (NM_003037)	+	-893	-826
	Mouse (NM_013730)	-	-887	-517
	Chimera mouse/60h/61h	+	-949	-744
	Chimera mouse/60h/61h/63h	+	-894	-879
CDV (AF305419)	Dog (AF325357)	+	-884	-780
	Mouse (NM_013730)	-	-1235	-1051
	Human (NM_003037)	-	-1073	-957
	Chimera mouse/63h	+	-1216	-877

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フラグメント分子軌道法の地球生態系解析への応用
－ウイルスヘマグルチニンとそれらの受容体の相互作用の解析－

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地球規模で拡大するウイルス感染症の基礎を理解するために、ウイルスのエンベロープタンパクと宿主の受容体との相互作用をフラグメント分子軌道法（FMO）により、JAMSTEC の地球シミュレータを用いて解析した。この解析で、我々はインフルエンザウイルスおよびモルビリウイルスの二つのウイルスに注目した。トリインフルエンザウイルスはシアル酸とガラクトースがα2,3 結合した受容体（α2-3 型）と親和性を有しているが、ヒトインフルエンザウイルスはα2,6 結合した受容体（α2-6 型）に結合する。我々は最近、ヒトへ感染することが報告されたトリ由来の H7N9 型インフルエンザウイルスのヘマグルチニン（HA）のヒトおよびトリ受容体への結合を解析した。FMO 法による相互作用解析の結果 H7N9 ウイルスの HA は通常のトリインフルエンザウイルスである H7N3 型ウイルスに比較して、ヒト型受容体に高い親和性があることが示された。これらの結果は、実験で得られた病原性のデータと一致しており、我々はさらに、トリ型あるいはヒト型インフルエンザウイルス HA と、トリあるいはヒトの受容体との結合親和性について、FMO 分析の結果を比較することで、分子機構の説明も試みた。

モルビリウイルス類はその HA が宿主動物の Signaling lymphocyte activating molecule (SLAM) を受容体に結合することで感染する。その仲間で研究が進んでいる麻疹ウイルス（MV）の HA とサルの SLAM の複合体は結晶化され立体構造が報告されていることから、その構造をテンプレートにして、HA-SLAM の立体構造を分子動力学的な計算により推定した。FMO 解析の結果推定された MV-HA と数種の哺乳類（ヒト、サル、マウス、イヌ、アザラシなど）の SLAM との結合親和性とこれらの哺乳類の MV に対する感受性は一致していた。しかし、まだ複合体の構造が報告されていないイヌジステンパーウイルス HA と幾つかの哺乳類の SLAM の間では、その両者は一致していないように思われた。そのような相違は、一次構造の類似度に依存した構造モデリングに一因があると思われ、複合体の立体構造を高精度で予測する工夫が必要である。

今回の研究から、ウイルスエンベロープである HA と宿主の受容体の結合の推定には、もし HA と受容体の立体構造が判明している場合には、FMO 法による解析でその親和性を推定することは、有効な方法であることが判明した。しかし、解析対象と類似の立体構造が明らかでない場合には、そこが問題となるため、今後、高精度で複合体構造を予測して相互作用解析を行うことが重要であることも明らかとなった。

キーワード: インフルエンザウィルス, モルビリウイルス, 受容体, フラグメント分子軌道法, ヘマグルチニン, Signaling lymphocyte activating molecule (SLAM)