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Coarse Grained Molecular Dynamics Simulation of Interaction between Hemagglutinin Fusion Peptides and Lipid Bilayer Membranes

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Abstract. Microscopic level interaction between fusion-peptides and lipid bilayer membranes plays a crucial role in membrane fusion, a key step of viral infection. In this paper, we use coarse-grained molecular dynamics (CGMD) simulations to study the interaction between hemagglutinin fusion-peptides and phospholipid bilayer membranes. With CGMD, we are able to simulate the interaction of fusion peptides with a relatively large piece of membrane for a sufficiently long time period, which is necessary for a detailed understanding of the fusion process. A conformation of the peptide with a kink at the level of phosphate group is obtained, consistent with NMR and EPR studies. Our results show that the N-terminal segment of the peptide inserts more deeply into the membrane bilayer compared to the C-terminal segment, as observed in previous experiments. Our simulations also show that the presence of fusion peptides inside the membrane may cause bilayer thinning and lipid molecule disorder. Finally, our results reveal that peptides tend to aggregate, indicating cluster formation as seen in many experiments.

AMS subject classifications: 74K15, 92C40, 65C99, 92D99

Key words: Coarse-grained molecular dynamics, fusion peptide, hemagglutinin protein, phospholipid bilayer, membrane fusion.

1 Introduction

Membrane fusion is one of the fundamental multi-cellular biological processes, inclu-

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ding fertilization, viral entry, release of hormones and rapid communication between neurons via neurotransmitter release and signaling [7,19,22,23,36,37]. Fusion of viral enveloped and cellular membranes, which allows the delivery of viral RNAs/DNAs into a host cell, is a crucial step for any successful viral infections and virus replications. While protein-mediated membrane fusion has been studied in some detail, the mechanism is not yet well understood. Improving our knowledge of membrane fusion may help scientists to find appropriate conditions for preventing viruses such as influenza, HIV, hepatitis from fusing to and thereby infecting human cells. Understanding the virus-cell membrane fusion may also provide a clue for designing new drug delivery methods.

Viral glycoproteins, such as hemagglutinin (HA) of influenza virus and gp41 of HIV1, have been identified experimentally as mediators for the fusion process related to viral infections [6,9,49]. As one of the best-studied fusion mediating proteins, HA consists of a trimer of individual monomers with HA1 and HA2 subunits, responsible for binding to the host cell membrane and inducing fusion, respectively. After binding, the virus internalizes into endosomes, where a low-pH (between pH 5 and 6) environment activates conformational rearrangements of the HA. During the conformational change, it reconfigures loops into helices. The subsequent translation and reorientation of the helix cause an elongation of the trimeric coiled-coil of the HA2, and the fusion peptide (consisting the first 20 amino acids of the HA2 N-terminal region) binds and inserts into a target cell membrane [4,5,41]. Only the fusion peptide, which is a highly conserved 20 amino acid sequence present in the HA protein [10,16,21,47–49] enters and interacts with the target membrane. Understanding this interaction is essential for a detailed understanding of the fusion mechanism.

There exist a large number of experimental studies on the fusion process and related conformational changes of HA protein and the structure of fusion peptides [1, 2, 11, 13–16, 18, 27–30, 42, 43]. However, very few mathematical and computational studies [20,25,38,45,46] on peptide-membrane interaction have been carried out. Experimental measurements using electron paramagnetic resonance (EPR) and nuclear magnetic resonance (NMR) have provided the structure of the HA fusion peptide inside bilayer membranes [16,18,28]. Due to limitations of their resolution, it is difficult to use these approaches to study the effect of the embedded peptide on bilayer integrity. As an alternative, full atomistic level molecular dynamics (MD) simulations have been carried out to determine the structure and the orientation of a HA fusion peptide inside a bilayer membrane [20,25,38,45,46]. However, MD is computationally intensive and existing simulation studies have been limited to a small portion of the bilayer (128 lipid molecules) with one peptide and short time duration (5-20 ns). On the other hand, it was shown that only a concerted effort of at least three to four HA-molecules (i.e., 9 to 12 fusion peptides) for a time period longer than 30 ns can lead to a successful fusion event [11]. Therefore, it is necessary to develop a more efficient method, which can simulate bigger sized bilayer with many peptides for a sufficiently large time period.

In this paper, we use a coarse-grained molecular dynamics (CGMD) simulation