Dissertation Project – 2nd Cycle

Project area: Biomolecular Simulation / Protein Modelling Lab / Biological Chemistry Division

Supervisor: Cláudio Soares and Diana Lousa

Duration: 1 year

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TITLE: Molecular determinants of the chikungunya virus fusion peptide activity

BACKGROUND

Chikungunya virus is a mosquito-borne virus, belonging to the alphavirus genus and Togaviridae family. This virus is named after the disease it transmits, which is characterized by high fever and severe joint pain. Chikungunya infections occur mostly in Africa and Asia, although a major outbreak affected the American continent in 2015. Currently, no effective treatment against this virus is available.

The chikungunya virus is encapsulated by a lipid membrane (envelope), which needs to be fused to the host plasma membrane to initiate the infectious process. Fusion is catalysed by the glycoprotein E1, a class II fusion protein. One important and conserved region of this protein, known as the fusion loop or fusion peptide, plays a crucial role in the fusion process, by inserting into and disturbing the host membrane. The structural and fusogenic properties of this peptide have been investigated by NMR, fluorescence and FRET-based methods.[1] However, the molecular details of the peptide-membrane interactions remain elusive. Additionally, the peptide structure was obtained in a lipid micelle and may change in a bilayer environment.

Our group has a large experience in the analysis of the interaction of fusion peptides with model membranes. In two recent works, we have used non-standard simulation techniques (self-assembly and bias-exchange metadynamics) to study the influenza fusion peptide.[2,3] The use of these techniques was paramount and allowed us to provide interesting new insights into the structure and activity of this peptide. More recently, we started studying the dengue fusion loop, which also belongs to a class II fusion protein. In the current project, we intend to use similar methodologies to analyse the chikungunya fusion peptide and compare the results with those obtained for other viruses, in order to obtain a broad description of the role of viral fusion peptides.

1. Mohanram H.., et al., 2**012**, *Biochemistry*, **51**, p. 7863–7872
2. Victor B. L., et al., **2015**, *Journal of Chemical Information and Modeling*, **55**, 795-805
3. Lousa D., et al., **2016**, *Scientific Reports*, 6:28099

OBJECTIVES

The main goal of this project is to characterize the interaction of the chikungunya fusion peptide with model membranes, using a molecular simulation approach. We want to address the following questions:

1- What conformations does the chikungunya FP adopt in water and in the membrane?

2- How does the peptide affect the membrane properties and promote fusion?

3- Is there a common mechanism used by different fusion peptides to promote fusion?

PROJECT DESCRIPTION

The student will learn and apply molecular simulation techniques to address the questions described in the objectives. Below we describe the main tasks of the project.

Task 1. Learning the basics of molecular simulation and literature review

The student will get familiarized with the basic concepts of molecular simulation and learn how to use the techniques that will be applied during the project. The student will also perform a literature review to get acquainted with the current state-of-the-art regarding the chikungunya fusion process.

Task 2. Simulations of the chikungunya fusion peptide

The student will perform simulations of the FP in water and in the presence of a membrane bilayer, using standard molecular dynamics and enhanced sapling methods, such as metadynamics. The effect of mutations will also be analyzed.

Task 3. Analysis of the results

The student will analyze and compare the energy landscapes of the WT and mutant fusion peptides. The effect of the peptides on the membrane properties will also be analyzed in order to shed light into the molecular determinants of the dengue fusion peptide activity. The results obtained will be compared with those obtained for other viral fusion peptides.

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TIMELINE (use fill tool for the cells)

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10
Task 1										
Task 2										
Task 3										
Thesis										

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