Unité de Virologie Structurale
Institut Pasteur

Group: Structural virology of bunyaviruses

Structural studies of the hantavirus glycoprotein shell

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Hantaviruses are rodent-borne viruses that produce two different life-threatening syndromes. Some of them have the potential to adapt to human-to- human air-borne transmission routes, increasing their epidemic potential. To our regret, we still do not have efficient treatments or vaccines. From a molecular perspective, hantaviruses are enveloped viruses with a segmented, ssRNA genome encoding for four structural proteins: a polymerase, a nucleocapsid, and two envelope glycoproteins termed Gn and Gc. The glycoproteins are responsible for the formation of the viral particle, interaction with the cellular receptor, and mediate viral fusion. Furthermore, because Gn and Gc are the only proteins exposed to the immune system, they are the sole target for neutralizing antibodies. All this makes them essential targets in the development of effective treatments to combat hantavirus.

These proteins have been extensively studied from a structural perspective. We know Gn and Gc form a metastable $(Gn/Gc)_4$ prefusion complex that further associate into lattices to form the mature virion (see the figure below). After receptor mediated endocytosis, the complex dissociates in response to the acidic pH and Gc acquire an extended conformation, projecting an hydrophobic segment that inserts in the cellular membrane. The process does not end here and Gc suffers a major structural reorganization, which leads to both membranes, cellular and viral, to approach and ultimately merge. The viral genome enters the infected cell and begins the viral replicative cycle. Despite much is known, there is much more that is unknow. The assembly and maturation are not understood, nor we do understand how hantaviruses interact with their cellular receptors or the neutralization mechanisms that some neutralizing antibodies use.

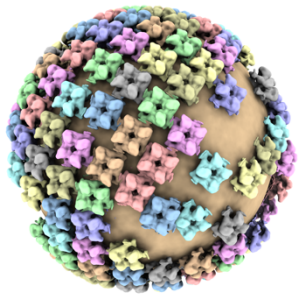

Figure 1. Model of the hantaviral virion obtained by a combination of x-ray crystallography and cryoEM (see refs 1 and 2)

In this project, we want to step forward and obtain structural and molecular information of some neutralizing antibodies in complex with the hantavirus spike by using crystallography, state-of-the-art cryo-electron microscopy and Bio-Layer Interferometry (BLI). We are looking for a motivated candidate who is interested in learning structural techniques in a competitive environment.

References to read

1. Guardado-Calvo P, Rey FA. The Surface glycoproteins of hantaviruses. ***Curr Opin Virol*** (2021)
2. Serris A, et al.. High-resolution description of the hantavirus surface glycoprotein lattice and its membrane fusion control mechanism. ***Cell*** (2020)
3. Jangra RK, et al . Protocadherin-1 is essential for cell entry by New World hantaviruses. ***Nature*** (2018)
4. Guardado-Calvo P, et al . Mechanistic Insight into Bunyavirus-Induced Membrane Fusion from Structure-Function Analyses of the Hantavirus Envelope Glycoprotein Gc. ***PLoS Pathog.*** (2016)