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Microbiology

Virus infection: may the (binding) force be with you?

by Martin Delguste [1] | PhD student; David Alsteens [1] | Professor

[1]: Louvain Institute of Bimolecular Science and Technology, Université catholique de Louvain, Louvain-La-Neuve, Belgium

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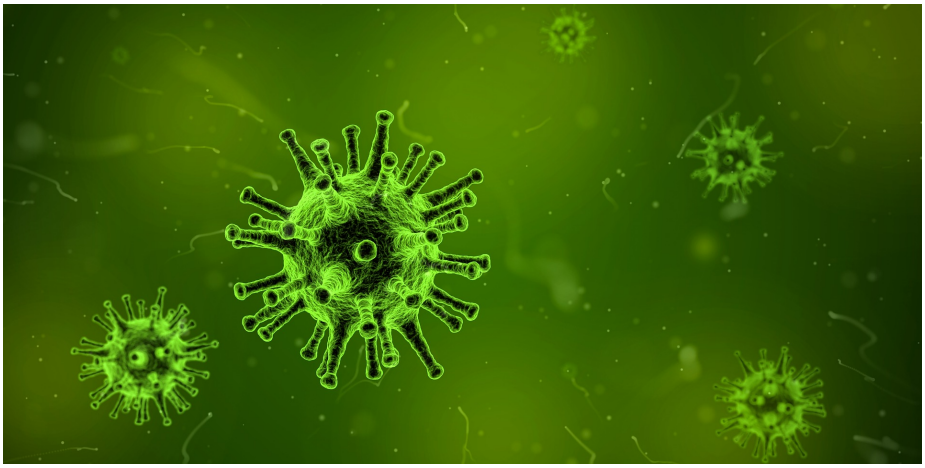
ABSTRACT

From touchdown to cell entry, a sophisticated microscopy can shed new light into the molecular mechanisms established by the viruses to hijack cellular barrier and enter the cell.



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Virus-related infections are diseases we have all experienced. From the common flu or cold to hepatitis, mononucleosis, and AIDS, viruses are the lead cause of numerous illnesses. Even though trillions of virus particles peacefully occupy our inner body, some others are real troublemakers. But why are those particles harmful to their gentle host?

To understand this, let's have a look at those intriguing species. Viruses are small particles invisible to the naked eye. Their main feature is that they are obligate intracellular parasites. This means that they absolutely have to enter inside a cell (from a human organ for example) to reproduce themselves. In fact, they hijack the cellular machinery to fabricate new virus particles. Thereby, the infected organ is unable to work correctly, which leads to virus-related diseases.

To gain access to the interior of human cells, viruses have developed several strategies. They use entry doors located on the cell surface. In order to reach these doors, viruses have first to attach to the cell surface. To do so, components from the virus surface called glycoproteins bind specific features of the cell membrane. This allows viruses to travel from the extracellular environment to the cell surface and reach the interior of the cell. There, thousands of copies of the virus will be fabricated and spread out to infect and colonize neighboring cells. This process will then repeat multiple times, leading to a pathological situation. But can we do something to stop these viruses from spreading?

In most cases, no. During viral infections that cannot be prevented by vaccination, one has just to wait until it is over and treat the symptoms of the illness. In some cases however, antiviral therapies can be used to block the viral life cycle. Yet, antiviral drugs

are only available for a limited number of viruses. Therefore, a better understanding of the mechanisms involved in virus infection could allow the development of new antiviral therapies.

In this study, we were interested in the attachment of a virus from the gammaherpesvirus family. In humans, these viruses are responsible for mononucleosis but also certain types of cancers and especially affect immunocompromised people. This virus carries multiple glycoproteins on its surface, which mediate the attachment to cells. However, the exact function of each glycoprotein is not fully understood. In this research, our goal was to study the role of the biggest glycoprotein, gp150, in virus attachment to its target cells.

We performed most of our study using an instrument called atomic force microscope (AFM). This tools works as a tiny fishing rod, at the end of which a virus particle can be grafted. By bringing the virus close to the cell surface and then pulling it away, the AFM is capable of measuring the binding force that allows one virus particle to attach to a cell surface. In addition to that, we used genetic engineering to create virus particles that do not display the glycoprotein gp150 at its surface. Thereby, we could compare the binding forces of a “normal” virus to one lacking gp150.

Surprisingly, our main observation was that virus particles lacking gp150 bound more strongly to cellular surfaces. We could furthermore determine that this increased binding strength was due to a higher number of viral glycoproteins interacting simultaneously with the cell. However, we observed that this increased binding capabilities of gp150-deficient viruses was detrimental for infection. We showed that virus particles lacking gp150 remained stuck on the cell surface, while normal viruses were able to enter. Indeed, as the gp150-deficient virus sticks too much to the cell, it is unable to move on the surface and search for its entry doors.

From these results, we could infer that the glycoprotein gp150 has a regulatory role in virus attachment. Gp150 reduces the number of simultaneously interacting glycoproteins, probably by covering their surface. Thereby, it allows the virus to bind with an adequate strength so that it can easily move on the cell surface to reach the doors and gain access to the interior of the cell.

This new discovery will certainly have an impact on the development of antiviral therapies. As we have highlighted the crucial role of gp150 in virus attachment, we believe that this feature will guide the design of new antiviral therapeutics. For example, drugs targeting gp150 could be developed to block the regulation of virus attachment, impede its entry into our cells and thereby stop the infectious process. This will allow treating viral infections faster than we actually do.