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Editorial

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The Lipid Rafts in *Caprine herpesvirus type 1*: Preliminary Study on Viral Infection *in vitro*

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Introduction

Caprine herpesvirus type 1 (CpHV.1) is an alpha-herpesvirus of the *Herpesviridae*, a large and various family of DNA virus encased in an icosahedral capsid and in an envelope composed of about a dozen viral proteins and glycoproteins. All herpesviruses have a relatively broad host range for cultured cells, and consequently, each of these viruses can use multiple cell surface receptors for entry [1]. Herpesvirus employes five major viral glycoproteins, designed gB, gC, gD, gH, and gLT as fusion machinery for virus entry, although additional receptors may also be required [1]. Cell entry receptors are required to trigger this fusion, but the molecule that herpesvirus glycoproteins associated with is not necessarily a protein [2]. Most, but not all herpesviruses, binding viral glycoproteins to glycosaminoglycans, usually heparan sulfate, on cell surface proteoglycans, that greatly increases the efficiency of viral entry, even if they may not be essential for virus infection. Since it has been supposed that the interactions of one or more viral glycoproteins with cellular receptors could trigger envelope-membrane fusion or cell-to-cell fusion [3,4], the identification of the viral and the cellular domains involved in the interaction of virus and cell were the objective of several studies.

The entry process has been studied in detail in many herpesviruses. The entry receptors discovered to date include herpesvirus entry mediator (HVEM), a member of the tumor necrosis factor (TNF) receptor family (nectin-1 and nectin-2), two members of the immunoglobulin superfamily, and specific sites in heparan sulfate generated by certain isoforms of 3-Osulfotransferases [1]. Extensive areas of the plasma membrane surface consist of lipid rafts, cholesterol-rich microdomains important for signal transduction, protein sorting, and membrane transport [5-8]. Membrane lipid rafts play a critical role in the life cycle of different viruses and in particular in the process of viral infection and in the entry of nonenveloped viruses, as well as of many enveloped viruses, in which accumulating evidences suggest that viruses entry may require cholesterol in either of the two membrane involved, or in both [9].

In a previous study, three fundamental phases of herpesvirus infection was analysed: binding, entry and post-entry. Interestingly, a productive CpHV.1 infection required different claim of cholesterol in cellular and viral membranes [10]. To corroborate the functions of the lipid rafts in the biology of CpHV.1 infection, the methyl-β-cyclodextrin (MβCD), a derivative of a cyclic oligomer of glucose with a lipophilic property, was employed *in vitro* to extract cholesterol out of membranes, to disrupt lipid raft formation on cells, and to block biological processes based on lipid rafts [7,8]. MβCD did not prejudice CpHV.1 binding to the Madin Darby Bovine Kidney (MDBK) cell line, but cell membrane cholesterol was required for CpHV.1 replication at the virus entry phase, and a dose-dependent reduction of the virus yield was observed after MβCD treatment. These experimental data confirm that cholesterol depletion was responsible for the decrease of CpHV.1 infectivity. To support the observation that decrease in the infectivity was the results of the cholesterol depletion, plasma membrane was replenished with exogenous cholesterol and the inhibitory effect was reversed. Furthermore, MDBK cells were treated with cholesterol sequestering drug after virus entry. The analysis revealed that virus replication was inhibited, but comparing this reduction with cells pre-treated with MβCD and then infected, the effect was moderate. This observation suggested that cholesterol is mainly required during virus entry rather than during the post-entry stage [10].

We might wonder why CpHV.1 infectivity was susceptible to MβCD treatment. The answer must be sought in the modality of envelope development of *Herpesviridae*. All enveloped viruses assemble their capsids in the cytoplasm and, budding from the plasma membrane, become enveloped. Viruses that mature in the nucleus, such as herpesviruses, must transport their nucleocpasid across the nuclear membrane. But herpesvirus capsids cannot move through nuclear pores, because of their size, and consequently, promotes a sofisticated mechanism. Herpesvirus capsids start primary envelopement by budding at the inner leaflet of the nuclear membrane and, to translocate into the citoplasm, they fuse the first coating with the outer leaflet of the nuclear membrane. In the cytoplasm, herpesvirus nucleocapsids acquire the envelope by budding into vescicles of the Golgi network and then are release from infected cells [11].

Another aspect emerge from these study and should be emphasized and required further investigations. The adsorption of viruses on the host cell receptors is the crucial phase in starting infection. Most cellular receptors was identified in glycoproteins, but also lipids and carbohydrates are employed by several viruses. Because alpha-herpesvirus entry is favored, if not dependent on, by interactions with more cell surface receptors, recently, heparan sulfate and new receptors was identified as co-receptors [1]. To date, receptors for CpHV.1 have not yet been identified, limiting the assumption that MβCD treatment prejudiced both the interaction between CpHV.1 with cell receptors and the expression of the receptors. Notwithstanding this is a suitable hypothesis to support and to deepen in the future, expecially because the identification of the host cell receptor is a crucial step in the start-up phase of the infection, and in the evolution and progression of the pathogenesis studies on CpHV.1.

The current investigations on CpHV.1 biology, have important implications, because they help to better understand the pathogenetic mechanisms of CpHV.1 infection, and several advantages are offered by this model. CpHV-1 vaginal infection in goats is reproducible, with evident herpetic lesions developing in the infected animals, as

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well as Human Herpesvirus 2 (HHV-2) causes in humans. Although mice have been largely used to study HHV-2 infection, goats may offer selective advantages over rodents [12], although major efforts have to be made to overcome the lack of species-specificy and the lack of detailed information on the immune system of this species. The development of assays to study CpHV-1-pathogenesis may significantly impact the field of HHV-2 research.

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