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A Commentary on Low pH Enhancing Zika Virus Infection

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About the Study

During transmission events through mucosal tissues, pathogens need to endure a diversity of contrasting environments to infect a new host. It is a requisite for sexually-transmitted pathogens present in semen to retain infectivity at the Female Reproductive Tract (FRT). This can be quite a challenge as FRT range between pH values of 4 to 6, and even several hours after semen deposition, which is slightly alkaline, the FRT remain acidic at pH values ranging between 6 and 7. While most viral pathogens cannot withstand acidic conditions for long time, sexually-transmitted viruses have the capacity to resist FRT acidic milieu. Zika Virus (ZIKV) is an arbovirus closely related to Dengue Virus (DENV) and transmitted by *Aedes aegypti* mosquitoes. However, during 2015-2016 ZIKV pandemic in the Americas, it was confirmed that unlike other arboviruses, ZIKV was capable of being transmitted after sexual intercourse. This observation challenged the paradigm of arbovirus-host interactions opening the question: What are the particular traits that allow ZIKV (and no other arbovirus) to be sexually transmitted? ZIKV can access and replicate in the testis, viral load in semen can reach levels ~100.000 fold higher than in blood and infectious virions can be recovered from semen several months after infection. But, as previously stated, it is a requisite for effective transmission that ZIKV retains infectivity after deposition into the FRT.

In Varese et al., the effect of extracellular acidosis on ZIKV infectivity was investigated using human FRT derived cell lines, monocyte-derived macrophages and cervix explants. Using a plethora of detection techniques (i.e. plaque-forming units, microscopy, flow cytometry and qPCR), it was shown that ZIKV not only retained infectivity when infections were performed at pH values similar to those found in the FRT (7.2 to 5.0), but infection rates increased ~10 to ~100 fold at pH value of 6.2. Enhancement of infection by extracellular acidosis occurred only when ZIKV and target cells were simultaneously exposed to low pH; the effect wasn´t observed neither when cells or ZIKV were pre-incubated at low pH and then neutralized prior infection, nor when infections were performed at neutral pH and then immediately after incubated at low pH. To sum up, binding experiments performed at 4ºC revealed that low pH positively modulated the interaction of ZIKV with target cells, and thus impacting on infection. Acidosis-mediated enhancement was present for both pandemic and pre-pandemic ZIKV isolates, but absent in DENV infection. This is of particular interest as ZIKV and DENV Envelope (E) proteins share high amino-acid sequence homology.

ZIKV E protein binding to target cells depends on many molecules and it is not clear which are the main receptors for ZIKV attachment. One common molecule used by several viruses for adsorption is Heparan sulphate (HS), which has been reported to modulate ligand interaction by protonation of histidine residues at low-pH (6.0-70). Experiments where HS was deprived from target cells indicated that HS-ZIKV interaction is modulated by low pH. Data so far indicates that when exposed to acidosis values comparable to those present in the FRT, either ZIKV Envelope (E) protein and/or HS suffer conformational changes that positively affects interaction between viral particles and target cells. Future investigations should center on better understanding the molecular mechanisms that grants ZIKV (and no DENV) the unique capacity of infecting the FRT and if this interaction can be manipulated as a therapeutic approach to prevent ZIKV sexual transmission.

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