HUMAN PLACENTAL TROPHOBLAST INFECTION WITH RIFT VALLEY FEVER VIRUS AND THE CELL CYTOKINE RESPONSE TO INFECTION

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Abstract

Rift Valley Fever Virus (RVFV) is a Mosquito borne virus (Bunyaviridae family) associated with hemorrhagic fever and abortion in ruminants and humans. Geographic distribution of the virus has expanded to most countries in African continent and in 2001 to Arabian Peninsula resulting in repeated epidemic and epizootic events. With abortion being the hallmark of RVFV infection, Understanding RVFV infection in human placental tissue can provide better insight into disease pathobiology.

In this study, three human trophoblast cell lines (A3, Jar & BeWo) were evaluated for permissiveness to RVFV infection. Furthermore, the viral capacity to spread by producing progeny viruses in trophoblasts was evaluated. The trophoblast response to infection was additionally assessed by measuring expression levels of important inflammatory cytokines in the cells (IL-1β, IL-6, IL-8, IL-10, IL15, CSF-2, IFN-g, Fas-L). Finally, two viral entrance mechanisms suggested for this virus were investigated in these cell models. Results suggested a high permissiveness of studied trophoblasts cell lines to RVFV leading to a severe cytokine response (IL-8 and IL-1β in Jar and increase in CSF-2, IL-1β, IL-6 and IL-8 in A3 cell line). Since these cytokines are vital in embryonic regulation and development, the severe effect of infection could potentially be part of pathogenesis of virus-induced abortion. When viral entry routes were investigated, heparan sulfate proved to be the main cell entry membrane protein used by RVFV. However removal of all galactosylamin transferases resulted in higher infection rate suggesting presence of other entry mechanisms in absence of galactosylamin transferase. Considering these results and the nature of primary trophoblasts in resisting infection, it is important to evaluate if the primary trophoblasts show the same or similar pattern of sensitivity to RVFV infection with both wild type and mutated viral strains. These findings merit further investigations regarding pregnancy response to infection, vaccination and treatment.

Key Words: RIFT VALLEY FEVER VIRUS; PLACENTAL TROPHOBLAST; CYTOKINE RESPONSE; ABORTION; HEPARAN SULFATE; GALACTOSAMYLE TRANSFERASE I
Popular Scientific Summary

Rift Valley fever is a disease caused by Rift Valley Fever Virus. The virus is transmitted through mosquito bite or direct contact with tissue or bodily fluids of an infected animal. Rift Valley fever has been associated with abortion in domesticated animals and humans. However, the symptoms can range from low fever to severe bleeding.

The virus’s geographic distribution has increased to most African countries and in 2001 it was found in Arabian Peninsula. The mosquito responsible for transfer of RVFV is very common across the world making this geographic distribution possible. Considering the severity of disease in pregnant women and possibility of further range increase it is important to understand the effect of infection on pregnancy.

For a virus to be able to cause severe disease, first it has to attach to human cells, second enter the cell and third produce many off-springs that themselves spread the disease. Abortion occurs if the virus is somehow able to cross the mother-fetus barrier and cause severe infection in the fetus or if the mother’s body responds in a way that would result in abortion. For the human fetus to get infected with RVFV, the virus has to first infect the tissue that connects the developing fetus to the uterine of mother. Trophoblast cells are the special cells located in this tissue that resist infection.

In this study, it was found that first, the virus can use multiple entry mechanisms, second that the virus was able to enter the trophoblasts and third the virus was able to produce many off-springs. Finally, it was found that the mother’s cell response is so severe that could cause abortion.

Understanding a problem, brings us closer to solving it or at least becoming prepared to deal with it. While the original studies connecting human abortion cases with RVFV were purely based on epidemiology and statistics, this study provided detailed confirmation that abortion can indeed occur due to RVFV infection. This study brings around the international attention required to fight viral infections. However, the first applications of this study would appear in how clinics treat pregnant women that live in high risk areas. But also by providing knowledge to the people living in the high risk areas regarding the disease and basic processes that could be used to avoid the disease. In a longer term, further studies are required to provide vaccines and better treatments.

Abbreviations:

- RVFV: Rift Valley Fever Virus
- MOI: Multiplicity Of Infection
- NS: Non Structural
- NSs: None Structural protein of s-segment
- PT: Placental Trophoblast
- IL-: Interlukine