



ENDOTHELIAL MODULATION DURING OROPOUCHE VIRUS INFECTION

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Abstract

In this project we showed that Oropouche virus (OROV) productively infect human umbilical vein endothelial cells (HUVEC). In addition, we demonstrated that this virus modulates the production of vasoactive cytokines, such as TNF- α and IL-6, and endothelial adhesion molecules, such as ICAM-1, e-selectin and eNOS. These data bring new insights how OROV can cross the blood-placental barrier.

Key words:

Arbovírus, Neuroinvasion, Immune response.

Introduction

OROV is an emerging arbovirus in Brazil associated with rash fever and neurological disorders in humans. OROV have circulated since 1960, with more than 500,000 cases already reported in the Amazon region (1). It is believed that this virus can cross the blood-brain and placental barriers to cause neurological. OROV was detected in cerebrospinal fluid from patients with meningoencephalitis, it is neurotropic and induce fetal malformations in animal models and there was increased cases of abortions in Amazon during OROV outbreaks (2). However, the mechanisms associated with endothelial crossing is poorly understood. Thus, this project aimed to characterize the effect of OROV on endothelial cells, regarding to expression of essentials molecules to leukocyte endothelial transmigration or to maintain the tight junctions between these cells.

Results and Discussion

OROV was able to replicate in HUVEC with two different MOI (multiplicity of infection), such as 0.01 and 0.001 (Image 1).

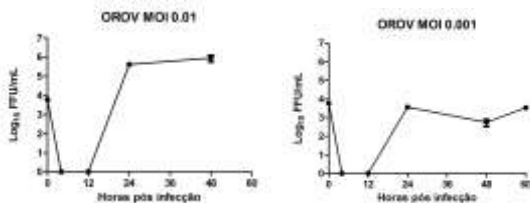


Image 1. OROV replication curve.

OROV induced the production of TNF- α , an inflammatory cytokine (3), in HUVECs after 4 hours post infection by ELISA. OROV also induced the expression of IL-6 determined by qRT-PCR (Image 2). These cytokines are vasoactive cytokines, associated with endothelial disruption in several models of infection.

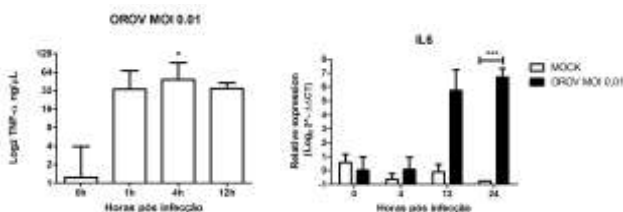


Image 2. TNF- α and IL6 quantification by ELISA and qRT-PCR

Finally, OROV infection in HUVECs promoted the transcription of genes essential to induce leukocyte endothelial transmigration or tight junctions disruptions, such as ICAM, e-selectin and eNOS (Image 3).

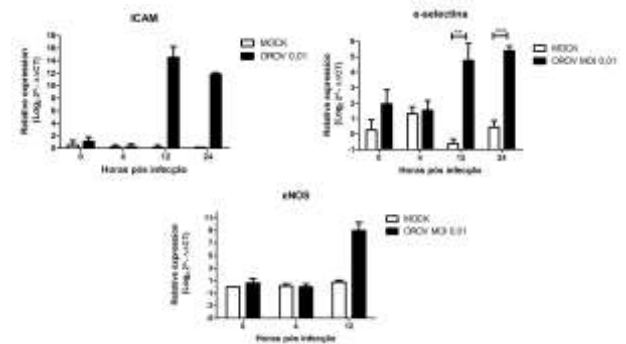


Image 3. ICAM, e-selectin and eNOS quantifications by qRT-PCR.

Conclusions

OROV can productively infect HUVECs, inducing the production of inflammatory cytokines and proteins essential to promote leukocyte transigrations and tight junctions leakage, key events during viral endothelial disruption. These data indicate that OROV can cross the endothelial barrier by 3 different mechanisms: 1. direct infection of endothelial cells and transport of generated viruses across basal lateral membranes; 2. spread of virus across endothelial cells tight junctions; 3. trojan horse pathway in with infected leukocytes in the blood migrate across endothelial cells (4).

Acknowledgement

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