

Role of Gas6, TAM receptors ligand, in the pathogenesis of Zika virus infection.

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Abstract

Zika virus (ZIKV) represents a public health challenge to Brazil and the rest of the world, especially because ZIKV infection has been linked to neurological sequelae, such as congenital fetal syndrome. Here, we aim to verify the role of Gas6 in the pathogenesis of ZIKV infection, by evaluating the expression of Gas6 and TAM receptors in patients infected by the virus with different degrees of disease severity, and infection of different human cells *in vitro*.

Key words:

GAS6, Receptors TAM, ZIKA Virus.

Introduction

The Zika Virus (ZIKV) is an arbovirus of the genus *Flavivirus*, transmitted through the bite of the *Aedes aegypti* mosquito, and it became a public health problem¹. In the Americas, there have been over 200.000 confirmed cases of Zika fever (ZF), 60% of those in Brazil alone¹. Although the infection is generally asymptomatic, recent data show the link between ZIKV infection to neurological sequelae, such as congenital fetal syndrome, for instance¹. Although it is far from clear all the mechanisms involved in the infection and how the ZIKV is able to cross barriers formed by endothelial cells (ECs), it has been shown that TAM receptors, especially Axl, act as a facilitator for the entry of the virus when it associates with the endogenous ligand Gas6 (Growth arrest-specific 6)². In regard, this project aims to verify the role of Gas6 in the pathogenesis of ZIKV infection. First, we evaluated the expression of Gas6 and TAM receptors in ZIKV-infected patients with different degrees of disease severity and in different human cells infected *in vitro*. These data will provide a better understanding of the relationship between the Gas6/TAM receptor axis with the pathogenicity of ZIKV, which may have important therapeutic consequences.

Results and Discussion

Until now we observed an increase of the Gas 6 levels in the serum of patients infected by ZIKV (Figure 1). This increase is even higher in patients that had developed neurological complication, such as encephalitis or meningitis, compared with non-neurological patients, suggesting a link between Gas6 expression and disease severity. Furthermore, ZIKV infection of human monocytes (THP-1 cell line) *in vitro* upregulates Gas6 secretion in a time and viral load-dependent manner (Figure 2). This indicates that ZIKV stimulates the production of its own ligand, which could increase the efficiency to infect cells.

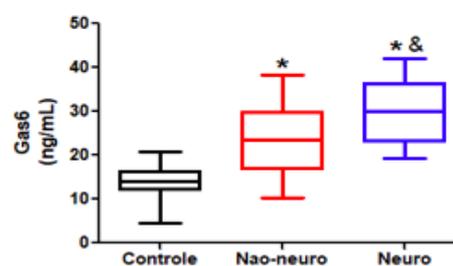


Figure 1. Gas6 concentration, in ng / mL, in serum of patients infected by ZIKV quantified by ELISA, in control patients (n=19), non-neurological patients (n = 30) and neurological patients (n = 13). * p <0.05 compared to the control group, & p <0.05 compared to the non-neurological group (Bonferroni's test).

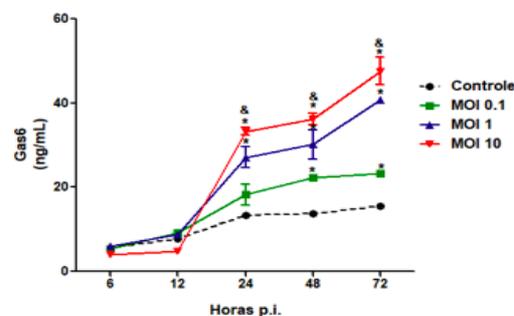


Figure 2. Concentration of Gas6 (ng / mL) in the supernatant of human monocytes (THP-1) infected by ZIKV at 6, 12, 24, 48 and 72 hours post infection. Monocytes were infected in different infection multiplicities (MOI): MOI 0.1, MOI 1, MOI 10. Representative of 2 independent experiments. * p <0.05 in relation to the control group, & p <0.05 in relation to the group MOI 0.1 (two-way ANOVA).

Conclusions

We demonstrated that Gas6 may have an important role in the severity of ZIKV infection, since its concentration is higher in neurological patients. However, it is not clear whether ZIKV infection itself can modulate the expression of its ligands, such as Gas6 and TAM receptors. Therefore, it is important to understand how these molecules are modulated and participate in the pathogenesis of the infection in humans.

¹ Zika Epidemiological Update, 27 April 2017. Pan American Health Organization / World Health Organization.

²MORIZONO, Kouki; XIE, *et al.* The Soluble Serum Protein Gas6 Bridges Virion Envelope Phosphatidylserine to the TAM Receptor Tyrosine Kinase Axl to Mediate Viral Entry. *Cell Host & Microbe*, vol. 9, no. 4, p. 286–298, 2011.