



Characterization of TIM and TAM receptors expression in placenta of pregnant women infected with Zika virus

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Abstract

The aim was to characterize TIM and TAM receptors expression in placenta of pregnant women naturally infected with Zika virus (ZIKV) during pregnancy. A systematic protocol for placental sampling was employed, collecting immediately after childbirth, from five different regions: umbilical cord, chorionic villus, chorionic plate, basal plate and amniotic membrane. 17 pregnant women presented symptoms, serological and/or RT-qPCR results compatible with arbovirus infection and their placenta were collected. The acute phase symptoms occurred during first trimester in 03 women, second trimester in 06, and during third trimester in 08. Two of the 17 newborn presented Congenital Zika Syndrome (CZS), evolving to neonatal death. 09 pregnant women had positive detection to ZIKV in the acute phase samples and, of the total placentas, 14 presented ZIKV positivity in different regions by RT-qPCR assay. There is no significant differences in the gene expression comparing infected and uninfected placentas regarding to TYRO3, AXL (TAM receptors) and TIM1 (TIM receptor) by RT-qPCR assay. In this way, apparently, ZIKV infection does not modulate TAM and TIM receptors expression in different placental regions. Thus, the results indicate that ZIKV can infect different regions of placentas of naturally infected pregnant women, and its detection in the placenta after several months of the initial symptoms suggests that this organ can be site for viral persistence during pregnancy.

Key words:

Zika virus, Placenta, TIM and TAM receptors

Introduction

Zika virus (ZIKV) is an emerging arbovirus of great impact in public health worldwide. The major 2015 and 2016 epidemics of ZIKV in Brazil evidenced the association between the infection of it in pregnancy and the development of neurological and morpho-functional fetal dysfunctions, in a condition known as Congenital Zika Syndrome (CZS). However, little is known about ZIKV infection in the different placental regions during natural infection in humans, and its association with the expression of receptors already described for this virus, such as TIM and TAM receptors. Thus, the aim of the study was to characterize the presence of the ZIKV and the expression of TAM and TIM receptors in several placental regions obtained from pregnant women naturally infected with ZIKV.

Results and Discussion

During the ZIKV outbreaks, several samples were collected from pregnant patients in the acute phase of infection and also from placentas after childbirth, in a stratified and systematic protocol, and storage at the Women's Hospital Biobank (University of Campinas). All pregnant women had their clinical history reviewed and analyzed. Placental samples were collected from five different regions: chorionic villus, chorionic plate, basal plate, amniotic membrane, and also from the umbilical cord. Samples were stored appropriately and then processed for future assays, with RNA extraction and cDNA synthesis performed. The ZIKV detection were made by RT-qPCR assay. Three receptors were listed for the analysis of the gene expression for RT-qPCR: TIM1 receptor - TIM receptor - and TYRO3 and AXL - TAM receptor. The endogenous control used for relative RT-qPCR for gene expression was YWHAZ. The results obtained were:

Infection first symptoms according to gestational trimester	
1 st trimester	3 (9.1%)
2 nd trimester	6 (36.4%)
3 rd trimester	8 (54.5%)
Delivery and consequences	
Vaginal	9 (52.9%)
Cesarean	8 (47.1%)
Neonatal malformations	2 (11.8%)
Neonatal deaths	2 (11.8%)
ZIKV RT-qPCR detection	
Acute phase samples	09 ZIKV positives (52.9%)
Placental samples	14 ZIKV positives (82.4%)

Chart 1. Data on acute phase infection, childbirth and perinatal outcomes and ZIKV detection.

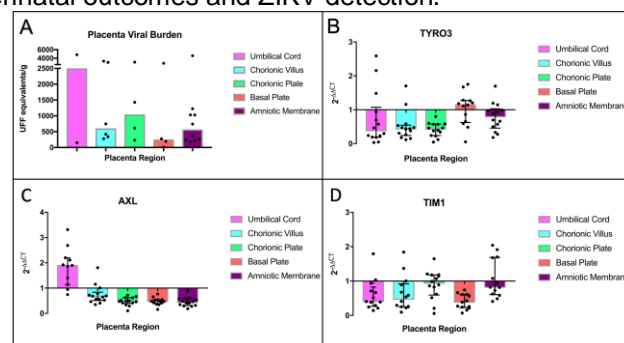


Image 1. A: ZIKV viral burden in different placenta regions. **B, C and D:** Gene expression of TYRO3 (**B**), AXL (**C**) and TIM1 (**D**) in different placenta regions. Bars represent median and error bars represent interquartile range. Each point represents an individual patient.

Conclusions

No significant differences in the gene expression of infected placentas to uninfected placentas regarding the receptors were evidenced by RT-qPCR assay. Therefore, apparently, ZIKV infection does not promote the modulation of TIM and TAM receptors in different placental regions. In addition, ZIKV detection in the placenta after several months of initial symptoms suggests that this tissue can be a site for viral persistence during pregnancy.

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