ORT_19 - Congenital Zika Syndrome is associated with interferon alfa receptor 1

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Introduction: Congenital Zika Syndrome (CZS) in a myriad of fetal abnormalities caused by Zika Virus (ZIKV). Nevertheless, it is not clear what maternal and/or fetal factors contribute to CZS outcome. Type I and type III interferons have been reported as the main antiviral factor in Zika and other flavivirus infections. Besides, single nucleotide polymorphisms (SNPs) in these genes regulate their expression and are associated with Hepatitis C, and Yellow Fever vaccination outcomes.

Objective: Here, we aimed to analyze whether interferon alfa receptor 1 (*IFNAR1*) and interferon lambda 2 and 4 (IFNL2/4) SNPs could contribute to CZS outcome and its functional consequences in ZIKV congenital infections.

Methodology: First, we selected *In silico* target *IFNAR1* and *IFNL2/4* SNPs performing Principal Components Analysis using EIGENSOFT 4.2 with data from 1000 Genomes Project phase 3, followed by ANNOVAR analysis. Then, we conducted a case-control study with 143 newborns and 153 mothers with confirmed ZIKV infection during pregnancy, and genotyped the selected SNPs by allelic discrimination. Case-control study was adjusted using a panel of 46-indels ancestry informative markers. Placenta from ZIKV-infected pregnant was analyzed by ZIKV PCR, histology and gene expression by Fluidigm microfluid qRT-PCR system.

Results: Newborns carrying CG/CC genotypes of rs2257167 in *IFNAR1* presented higher risk of developing CZS (OR=3.58; IC=1.42-9.04; Pcorrected=0.0225). No association between *IFNL2/4* SNPs and CZS was observed. Placenta from CZS cases displayed lower levels of *IFNL2* and *ISG15* along with higher *IFIT5*. The rs2257167 CG/CC placentas also demonstrated high levels of *IFIT5* and inflammation-related genes.

Conclusion: Here we found CZS to be associated with exacerbated type I IFN and insufficient type III IFN in placenta at term, forming an unbalanced response modulated by the *IFNAR1* rs2257167 genotype. These findings shed light on the host-pathogen interaction focusing on the genetically regulated type I / type III IFN axis that could lead to better management of Zika and other TORCH (Toxoplasma, Others, Rubella, Cytomegalovirus, Herpes) congenital infections. Additionally, custom pharmacological interventions could be used to modulate immunity and inflammation towards protective responses.

Keywords: Congenital Zika Syndrome; Interferon; Placenta