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The immunopathogenesis of Zika virus: an overview

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Dear Sir,

Zika virus (ZIKV) is a single- stranded RNA virus and mosquito-borne flavivirus. In the recent years, Zika virus infection as a re-emerging infection is responsible for the major global health problem. Several routes of ZIKV transmission have been identified; vectors (*Aedes mosquitoes*) bite, urine, blood, saliva, sexual contact, breast feeding, vertical transmission. Many of studies showed that more than 80% of ZIKV infections are asymptomatic [1]. When symptomatic disease occurred its symptoms include fever, headache, cervical lymphadenopathy, maculopapular pruritic rash, arthralgia, myalgia and pain behind the eyes. Moreover, congenital Zika virus infection with and without microcephaly or other central nervous system (CNS) anomalies and Guillain-Barre Syndrome (GBS) are relevant complications of this infection. There are no specific treatment options or vaccine for Zika virus infection. Therefore, the study of the pathogenesis of Zika virus can help resolve the challenges in treatment and prevention. Despite numerous studies on pathogenesis, many factors involved in infection and immune system response are somewhat unknown.

The skin (keratinocyte, Langerhans cell, fibroblast) is the primary inoculation site of ZIKV, and then this agent spreads to lymph nodes, blood and also CNS, muscles and fetus. There is need to explain that AXL receptors, a receptor tyrosine kinase mediating inflammatory processes, as ARK, Tyro7 and JTK11, have an important role in viral influx to skin cells [2]. ZIKV caused to enhancement in the expression of melanoma differentiation-associated gene-5 (MDA-5), retinoic acid-inducible gene-I (RIG-I) and Toll-like receptor 3 (TLR-3) which are innate immune responses to RNA virus infections. So that, ZIKV-containing vesicles displace $Rab5^+$ endosomes and induce the TLR3 leading to suppression of the innate immune system. As previously mentioned, some of the serious side effects of the infection are several malformations of CNS like microcephaly or GBS as an autoimmune disease with paralysis. ZIKV can cause apoptosis of trophoblast cells which leads to the destruction of the placental barrier and then virus entry to the fetus. Based on these events, significant increases in amount of IL-6, IL-8, vascular endothelial growth factor (VEGF), and granulocyte colony-stimulating factor (G-CSF) have appeared in the amniotic fluid such that as these cytokines cause the cell death in the fetal nervous system.

ZIKV also activates factors engaged in the inflammatory response (CCLx), B-cell-mediated immunity (ICOS), the modulation of T-cell-mediated immunity (TAP2), and the regulation of cytokine production (IRF8). Being together of the mentioned immune factors leads to strong inflammatory response and major tissue damages, that these can confirm this infection can cause GBS [3]. Along with all of the above regarding the harmful effects of the virus, the human immune system also has some functions. So that, some researches in ZIKV infection showed that activation of T cells subsets (Th1, Th2, Th17) happened, and also upregulation of IFN gene expressions like IFN-α and IFN-β, lead to type I, II and III interferons restrained viral replication [4]. The ability of CD4+ T cells to produce pro-inflammatory cytokines and help to the antibody response alongside with the protective role for CD8+ T cells are confirmed in ZKV infection. Thus, a more understanding of interactions among ZIKV and immune system of the host can clear the potential guidance for developing ZIKV antiviral therapies or vaccines.

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