Emerging & re-emerging infectious diseases

A single amino acid substitution in NS5 protein enhances transplacental transmission of Zika virus

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Background: The emergence of Zika virus (ZIKV) in the Americas has aroused global concern due to its unexpected ability to cause congenital diseases in the context of infection during pregnancy. Previously, we have demonstrated that a single amino acid substitution (S139N) in the prM protein of ZIKV enhances viral neurovirulence and contributes to fetal microcephaly. Yet, how ZIKV crosses the placental barrier to target the fetal brain remains largely unknown.

Methods and materials: Phylogenetic and molecular clock analysis of all ZIKV epidemic strains was performed to identify the newly developed adaptive mutations. Recombinant ZIKV carrying these specific mutations were generated by using standard reverse genetic technology, and characterized with well-established in vitro and in vivo models in comparison with wild type ZIKV. The cytokine profiling was assayed in pregnant mice infected with the mutant virus or wild type ZIKV, and further validated with extensive biochemical assays and animal experiments.

Results: A unique amino acid substitution (M2634V) in the NS5 protein of ZIKV arose in 2014 and stably maintained in the Americas. The M2634V substitution did not affect viral replication in cultures and neurovirulence in neonatal mice, recombinant ZIKV with the M2634V mutation significantly enhanced the transplacental capability and resulted in more severe fetal growth restriction in multiple pregnancy mouse models. More importantly, this single M3634V mutation significantly increased the production of IP-10 which subsequently enhanced ZIKV infectivity in mouse placenta.

Conclusion: Our results demonstrate that the adaptive mutation M2634V enhances the vertical transmission of ZIKV by augmenting the secretion of IP-10 during pregnancy. This novel finding, combined with previous results, illustrates the dynamic process how ZIKV gradually acquired multiple adaptive mutations that enhanced viral neurovirulence and transplacental infectivity, and finally led to the emergence of congenital Zika syndrome cases in the Americas.

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