Maternal and fetal immune factors influencing Zika virus congenital syndrome

Zika virus (ZIKV) causes a mild febrile illness in adults, yet is of greatest concern because it can vertically transmit from mother to fetus. The fetuses of infected pregnant women are at risk for Zika congenital syndrome (ZCS), which can involve microcephaly, brain calcifications, absence of brain gyri, and other neurological defects. Emergence of ZIKV in French Polynesia in 2013 and Brazil in 2016 coincided with a sharp increase in cases of microcephaly and the viruses that were isolated were determined to be of a new “Asian” lineage, contrasting the milder “African” lineage strains. Using a mouse model of vertical transmission of ZIKV, we determined that both Asian and African lineage ZIKV strains induce ZCS involving disproportionate microcephaly, but that Asian lineage strains, including an isolate from Singapore, induce more severe neurological defects owing to their preferential targeting of neural progenitor cells and suppressed activation of microglia in the fetal brain. Microglia were determined to be neuroprotective in this model and their depletion led to enhanced infection and neuroinflammation in the fetal brain. Furthermore, we found that in mice and primates, maternal antibodies that are specific for the closely related virus, dengue, and cross-reactive to ZIKV can enhance fetal infection and ZCS severity in a mechanism dependent on ZIKV/immune complex translocation across the placenta and into the fetus. These findings show that both maternal and fetal immune factors can influence ZIKV infection outcomes and disease severity in fetuses.

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