Ziika Pathogenesis

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ZIKV Pathogenesis - human

Up to 80% asymptomatic/subclinical infections

Symptoms include rash, fever, myalgia, headache, and conjunctivitis

Disease is self-limiting (~1 week), hospitalization rare

Fatal ZIKV is seen in patients with underlying health conditions (sickle cell anemia, immunodeficiencies)

Guillain-Barré Syndrome, rare complication

Arzuza-Ortega et al., (2016). Fatal Zika virus infection in a girl with sickle cell disease, Columbia. EID 22(5).
25-yr-old Slovenian woman, traveled to Brazil

Suspected ZIKV infection @ week 13 gestation. Sonogram at 32 weeks showed microcephaly and retarded intrauterine growth. Terminated at week 32.

Gross pathology of brain showed multiple calcified foci, poorly developed basal ganglia, open sylvian fissues and dilated lateral ventricles.

Only brain was positive by RT-PCR (tested placenta, heart, lung, liver, spleen, kidney, thymus and skin)

Complete genomic RNA sequenced (groups with other Brazilian isolates)

Current Gaps in Knowledge

Timing of viremia with symptoms. Viremia in asymptomatic individuals?

What triggers Guillain-Barre syndrome?

Factors associated with fatal adult ZIKV infection.

Causal link of ZIKV infection to development of microcephaly (MC)?
  Timing?
  Attack rate?
  Role of asymptomatic infection?

Role of sexual transmission?
Animal Models

NHP: First isolated in 1947 from rhesus macaques in the Zika Forest, Uganda during a campaign to identify yellow fever (Rockefeller Foundation). 6 sentinel caged rhesus macaques were placed in the canopy. One NHP, No766, had a fever of 39.7°C. Isolated blood on day 3 of fever (ZIKV 776 strain). Inoculated Swiss-Webster mice IC- all showed illness.

Mice: young mice (<14 days old) highly susceptible. Adult mice infected in periphery are resistant. Adult mice infected IC are susceptible, but requires murine passages for consistent phenotype.

ZIKV in white mice

Swiss albino mice (neonates)
IC injections with a filtered “10 per cent” solution of isolates obtained from NHP sera or mosquito homogenate. Death was accompanied by paralysis.

Swiss albino mice (adults)
Isolate 766 showed 100% mortality by passage 16
Isolate 758 showed 100% mortality by passage 15 (incubation time = 5 days.) By passage 50-59, incubation time = 4 days. Stable phenotype up to pass 115.

Ae. africanus-isolated virus produced illness in mice (inactivity and ruffled coat) that lasted up to 30 days for some, recovery common. No virus isolation in chronic cases.

CD1 and C57Bl/6 mice are resistant to development of ZIKA disease

3-week-old CD1 mice, mixed gender
Cambodian 2010 (Asian lineage) isolate- FSS13025
Subcutaneous infection, $1 \times 10^4$ pfu

CD1 mice and C57Bl/6 (not shown):
- Do not show signs of illness
  - Hunched posture
  - Ruffled fur
  - Lethargy
  - Neurologic disease
- Mice do not lose weight
- Viremia not detected (LOD = 100 pfu/ml serum)
- Differences in weight not significant (ANOVA)
ZIKV infection in immuno-deficient mice

3-, 5-, 11-week old A129
1x10^5 pfu/mouse
Intraperitoneal injection

Daily observation for signs of illness
Weight taken
RO bleeds for viremia and/or seroconversion*
Necropsies for predetermined and moribund mice

*b Seroconversion results pending
Disease in A129 is age-dependent

* Sacrificed due to IACUC endpoint triggers (>20% weight loss)

# = not taken, * = undetectable

Rossi et al., (2016). Submitted for publication
Organ titers in 3-week A129 mice

High titers observed in spleen, testes and brain.

Mild splenomegaly observed on day 3.

Neurologic disease (tremors, loss of balance, partial hind limb paralysis) observed moribund mice.

Neurologic disease more severe in 3-week-old AG129 (“toe-walking” and loss of motor coordination).

Critical issues

• Further evaluation of the A129/AG129 model (or other k/o)
• Evaluate NHPs as model of infection and disease
• Maternal transmission models
• What is the role of symptomatic ZIKV infection on congenital abnormalities (MC)?
  - transplacental infection
  - *in utero*
  - sexual transmission
• What is the role of symptomatic ZIKV infection on neurologic (GBS) and other abnormalities?
• What is the role of asymptomatic ZIKV infections in development of MC, GBS and other abnormalities?
• What is the role of co-morbidities in clinical outcome of disease?
• What are the differences between African and Asian lineages?; adaptive evolution?
• How host genetics affect clinical outcomes?
• What is the role of intrinsic ZIKV virulence factors? Viral load?
• What is the role intra-host (vertebrate and vector) ZIKV genetic variation (quasispecies) in severity of clinical outcomes and transmission?
• Are there differences in clinical outcomes of ZIKV infections due to vector vs sexual transmission?
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