Understanding Zika virus disease pathogenesis

Michael S. Diamond, M.D., Ph.D.

Washington University School of Medicine
Departments of Medicine, Molecular Microbiology, Pathology & Immunology
Center for Human Immunology and Immunotherapy Programs

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Zika virus is a Flavivirus

- *Flaviviridae*; Flavivirus (and HCV)
- Enveloped (+) sense RNA virus
- Mosquito/tick-transmitted
- Encephalitis, shock syndrome, liver failure

Zika virus
Dengue virus
West Nile virus
Japanese encephalitis virus
Yellow fever virus

*Zika*-induced microcephaly

* Dengue: 390 million infections each year

*~50,000 WNV cases since 1999*
Zika virus is a flavivirus that is closely related to Dengue virus.
Zika virus: Is its pathogenesis related to other flavivirus infections?

**Encephalitic flaviviruses:** West Nile, Japanese, and tick-borne encephalitis viruses

- Spread to the brain and spinal cord and infect neurons leading to injury and cell death
- **Clinical outcome:** encephalitis, meningitis, paralysis

**Hepatotropic flaviviruses:** yellow fever virus

- Can infect cells in liver and cause acute liver (and kidney) injury
- **Clinical outcome:** Acute liver and kidney failure

**Hemorrhagic fever and shock syndrome:** Dengue virus

- Infects myeloid cells (monocytes/macrophages/dendritic cells) and produces high levels of pro-inflammatory cytokines in blood/tissues
- **Clinical outcome:** Shock syndrome (hemodynamic instability), bleeding

**Zika virus:** Microencephaly, Guillain-Barre syndrome: Infects neurons (?)
West Nile virus pathogenesis: crossing the blood-brain barrier and infection of the brain and spinal cord.
Dengue virus pathogenesis: antibody enhancement of myeloid cell infection, and vascular leakage syndrome

St John 2013, Nat Rev Micro

Vascular symptoms:
- Hypovolaemia
- Low blood pressure
- Shock

Hepatic injury
- Fluid pooling in body cavities
- Gall bladder thickening
- Haemorrhaging within organs

Vomiting
- Intestinal bleeding

DV-infected monocyte

DV-specific Ab

Enhanced uptake/infection via FcγR

Cytokines
- NS1 antigenemia

Four DV serotypes: DV1/DV2/DV3/DV4

Abs against one serotype do not neutralize a second serotype

2nd infection can be worse

St John 2013, Nat Rev Micro
Zika virus: lack of data in animals models (few studies)

1947
Zika Forest

1976


1947
Zika Forest

T = 40°C
Normal Normal Normal Normal Normal

No disease in cotton rats, guinea pigs, rabbits

Rhesus macaques

Virus passaged
From mouse via injection
of brain homogenate into brain

Virus found in
Brain/spinal Cord
only

Caused paralysis
Neuronal degeneration

Virus MR 766

Blood Sample
D3 of fever

Inject blood
Into brain

All mice get sick
at day 10

Infected newborn mice with ZIKV
Infected 4 week-old mice with ZIKV

Mice died: no description

Blood Sample D3 of fever

Infected newborn mice with ZIKV
Zika virus disease pathogenesis

Urgent needs

• Animals models of infection and disease pathogenesis with circulating strains
  - Mouse models
  - Non-human primate models

  Infection and virus dissemination, Guillain-Barre model
  Maternal transmission models

• Longitudinal studies of human disease
  - Where is the virus?
  - What is the nature of the injury (pathologic studies)?
  - Why only in some people?
Zika virus microcephaly

Microcephaly – recent case reports confirm Zika as cause

Paper #1 – Two newborn with microcephaly died soon after birth
Two miscarriages

Results: Brains positive for Zika virus RNA (only brains): (4/4)
Genetic sequence of Zika virus obtained
Viral protein seen in brain tissue (2/4)
Tissue damage only in the brain

Paper #2 – Pregnancy terminated due to severe brain disease of fetus

Results: Viral protein seen in the brain
Viral RNA detected and sequenced (complete Zika genome)
Infection and injury in neurons
Tissue damage in brain and spinal cord

Zika virus: Unanswered pathogenesis question #1

How does *in utero transmission* occur and why is Zika virus different than other flaviviruses?

More like hepatitis C virus (5-10%: pre-antivirals)

Risk factors: Viral load in blood

Possible infection of placental cells or trophoblasts
Zika virus: Unanswered pathogenesis question #2

Does pre-existing **Dengue immunity** affect Zika virus disease severity?

- Anti-Dengue antibodies cross-react with Zika virus
- Anti-Dengue antibodies bind but do not neutralize Zika virus
- Antibody-antigen complex binds to FcγR
- Zika virus now replicates more efficiently in FcγR expressing myeloid cells

*Adapted from Murphy 2011 Ann Rev Imm*
Zika virus: Unanswered pathogenesis question #3

What is the basis for **Guillain-Barre syndrome** after Zika virus infection?

GBS caused by destruction of myelin around nerves: demyelination

- Paralysis
- Tingling in arms and legs
- Muscle weakness
- Damaged myelin

**Possible mechanisms**

- Immunopathology due to viral antigen mimicry of a host protein
- Virus targets neurons/glial cells (tropism change compared to African strains?)
- Association with prior or concurrent immune response to Dengue
Zika virus: Pathogenesis summary