Clinical and immuno-pathological aspects of Chikungunya infection

“Immunopathology & intervention strategies” Panel

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Immunopathology and intervention strategies

• How does CHIKV cause disease?

• What is known about the immunological responses and pathophysiological events of CHIK in the human host?

• What approaches are being pursued in terms of development of therapeutics as anti-virals or vaccines for CHIK?

• What impact would an antiviral drug have on pathogenesis?
How does CHIKV cause disease?

- Clinical data
  - Fever, arthralgia, myalgia, rash
  - Severe forms: encephalopathy, elderly and neonates
  - Febrile arthralgia + lymphopenia < 1000; PPV > 80%

- Lessons from the mouse animal model and histopathological analysis of human tissue samples
  - Infected tissues are those in which symptoms manifest
  - Fibroblast are major target cells
  - Tissue envelopes are particularly targeted
  - Viral dissemination to the CNS, with CSF, meninges and ependyma being infected
  - CNS access via choroid plexuses, but not brain microvessels
  - No apparent neuropathology
  - No placental infection per se, but per-natal vertical transmission through placental breaches

Staikovski et al., submitted
Absence of type I interferon receptor (IFNAR) confers susceptibility to CHIKV

In IFNAR\(^{+/−}\), CHIKV infects only tissues classically symptomatic in humans
\(\rightarrow\) a model for mild infection

In IFNAR\(^{−/−}\), CHIKV disseminates to the CNS (as in neonates)
\(\rightarrow\) a model for severe infection

CHIKV infects fibroblasts of skeletal muscle

Mouse primary fibroblasts

Endomysium

Epimysium

Myotendinous insertion

Endomysium

Laminin
CHIKV
Hoechst

Coll IV
CHIKV
Hoechst

CHIKV infects fibroblasts of the joint capsule and the dermis

Similar cell tropism in human infected tissues

CHIKV infects choroid plexuses and disseminates to the meninges and ependymal envelopes

CHIKV-infected IFNAR-/- mouse

CHIKV does not directly target the placental barrier

Materno-fetal transmission assay in IFNAR−/− mice

- CHIKV not detected in human placenta
- Viral transmission only around the term
  → The fetus is most likely infected via labor-induced placental barrier breaches rather than actual placental infection

No CHIKV infection of the syncytiotrophoblast barrier

What is known about the immunological responses and pathophysiological events of CHIK in the human host?

- **Critical role of type-I IFN**
  - IFNAR, IFNAR-WT chimeras

- **Adaptive immune system not critical** to control infection
  - Viremia declines before the appearance of antibodies

- Generation of protective and in vitro/in vivo neutralizing antibodies in human and mice

- Possible role of macrophages in the inflammatory response accounting for post-acute symptoms (as for RRV)
What approaches are being pursued in terms of development of therapeutics as anti-virals or vaccines for CHIK?

∂ Severe forms and encephalopathy in elderly and newborn

∂ Correlation between viremia and severity

∂ Attempt to decrease viral load *in vivo*
  - antiviral, vaccines
  - Immunotherapy and immunoprophylaxis
What approaches are being pursued in terms of development of therapeutics as anti-virals or vaccines for CHIK?

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**Strategy:**

1. Harvest human immune plasma from convalescent individuals
   - selection based on clinical criteria, confirmed by Elisa

2. Purify IgGs from these pooled human plasma samples
   - according to a standard purification process used to produce a commercial polyvalent human IgGs preparation

3. Test for antiviral therapeutic and preventive activity
CHIKV-IgGs therapeutic activity

IFNAR\(^{-/-}\)
10 PFU CHIKV

WT NN
10\(^6\) PFU CHIKV

Couderc et al. JID, in press
What approaches are being pursued in terms of development of therapeutics as antivirals or vaccines for CHIK?

- **Preventive and therapeutic effect of polyclonal IgGs purified from convalescent patients**
  - Ready to be tested in human

- **Understanding of CHIKV basic virology**: entry and post entry steps to help design inhibitors of viral attachment, envelope fusion, decapsidation and replication

- **E1E2** as antigens for **vaccine development** (anti E1E2 IgGs are neutralizing)

- **Candidates** can be **tested** easily in our **mouse model**
What impact would an antiviral drug have on pathogenesis?

– High viremia is associated with severity
  • Lowering viremia would most likely lowers symptoms

– Anti-inflammatory drugs may reduce post-acute symptoms