Chikungunya virus tissue and cell tropisms and host factors influencing disease severity
Human infection

- Flu-like syndrome
- Myalgia, arthralgia, rash
- Severe forms
  - Neurological symptoms
  - Maternal-fetal transmission

Objectives

- Pathophysiology of the infection
  - Cell and tissue tropisms
  - Viral access to the CNS and fetus
CHIKV pathogenicity is age-dependent in mice

Mortality in WT mouse B6 adults and neonates

Tissue tropism in WT mouse B6 neonates
The absence of type I interferon receptor (IFNAR) confers a susceptibility to CHIKV infection.
Tissue tropism in adult mice

In IFNAR+/-, CHIKV infects only tissues classically symptomatic in humans → model for mild infection

In IFNAR-/-, CHIKV also disseminates to the CNS (as in neonates) → model for severe infection
Cell tropism in liver

CD31
Endothelial cells

F4/80
Macrophages

CHIKV
Merge

[Imagery showing staining of CD31 and F4/80 in liver tissue with CHIKV and merge views]
CHIKV in endothelial cells
CHIKV in Küpffer cells
CHIKV in fibroblasts of skeletal muscle

Mouse primary fibroblasts

- Viral titer (TCID50/ml)
  - endomysium
  - epimysium
  - spleen

Vimentin

Coll IV

CHIKV

Hoechst

Epimysium

Perimysium

Endomysium

Vimentin

CHIKV

Hoechst

Epimysium

Endomysium

Muscle endomysium

Col IV Chik Dapi
CHIKV in fibroblasts of the joint capsule
CHIKV in fibroblasts of the dermis
Similar cell tropism in infected human tissues

derm

muscle fascia

joint
Viral dissemination to the CNS

Anatomy of the blood-brain barrier

- Choroid plexuses
- Blood-CSF barrier
- Brain parenchyma
- Brain microvessels
- Blood-Brain parenchyma barrier
- Cerebrospinal fluid
- Fenestrated endothelium
- Astrocyte
CHIKV targets the choroid plexuses…

Mouse choroid plexuses

Primary choroid plexus epithelial cells
...but not microvessels endothelial cells nor the brain parenchyma
CHIKV in the meningeal and ependymal envelopes

Meninges

Brain parenchyma

Ependyma
Model for CHIKV invasion of the CNS

Fits with the presence of virus in the CSF of human patients with CNS symptoms
CHIKV does not directly target the placental barrier

Materno-fetal transmission assay in IFNAR-/- mice

<table>
<thead>
<tr>
<th>Virus titer (TCID50/ml or g)</th>
<th>Mother 1</th>
<th>Mother 2</th>
<th>Mother 3</th>
<th>Mother 4</th>
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<tr>
<td>maternal serum</td>
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<td>fetuses</td>
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Susceptibility of human syncytiotrophoblast to CHIKV infection

- Virus 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
Conclusion

1. CHIKV disease severity depends on age and type I IFN signaling:
   - partial abolition of type-I IFN signaling → model of mild disease characterized by muscle and joint involvement (as in human adults).
   - neonates or absence of type-I IFN signaling → model of severe disease with viral dissemination to the CNS (as in human neonates and adults with underlying conditions).

2. The liver is the first target organ in IFNAR mice: Kupffer cells and endothelial cells are infected.

3. In tissues associated with classical symptoms in human, the fibroblast is the principal target cell of CHIKV in mouse models as well as in humans.

4. CHIKV accesses to the CNS via the choroid plexuses, but not the brain microvessels. Meninges are infected but parenchyma is not.

5. The placenta is not permissive to CHIKV infection.
Future directions

- Early stage of the infection in mice

- Factors underlying adult mouse non permissiveness

- Identification of the molecular determinants governing CHIKV tissue and cell tropism:
  → Cell-specific surface receptor(s) ?
  → Cell-specificity of the IFN response shaping cell permissiveness ?
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