Zika virus NS1: association with virus infection and immune system

Yi Shi
Institute of Microbiology, Chinese Academy of Sciences
shiyi@im.ac.cn
What is Zika virus?

- Zika virus belongs to flavivirus family
- Transmission mainly by Aedes aegypti
- Clinical syndrome: fever, maculopapular rash, conjunctivitis, joint pain
- Classified into African and Asian genotypes by phylogenetic analysis
Zika virus -- "brother" of dengue virus
ZIKV infection

Microcephaly

Guillain-Barre Syndrome (GBS)

Cases of ZIKV and GBS, Colombia. EW 40/2015-4/2016 (from Ministry of Health of Colombia)

Zika virus exists in immune-tolerant regions

- The structure of placenta determines that the material exchange between mother and fetus is indirect.
- Zika virus must penetrate the placenta to infect fetus.
- Zika virus was found in the brain of fetus.
- Zika virus was also found in semen, lasting for a long time, and also in eyes.
Replication cycle of flavivirus

- Receptor binding and endocytosis
- Acid-catalyzed fusion and uncoating
- (+) vRNA
- Polyprotein translation
  - Transit to ER and processing
- CAP
- Membrane-bound RNA replication
  - (+) vRNA
  - (-) RNA
- Virus maturation
- Mature virion
- Nucleus
- ER
- TGN
- Golgi
Genome and polyprotein of Zika virus
Zika virus NS1 protein and disease pathogenesis

Zika virus infects cells

secrating NS1 protein
NS1 within the infected cell

Protective activity of anti-NS1 MAbs

<table>
<thead>
<tr>
<th>Antibody or control</th>
<th>% Surviving mice</th>
<th>No. of mice</th>
<th>P value</th>
<th>Antibody source</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBS</td>
<td>17</td>
<td>60</td>
<td>0.29</td>
<td>PUR</td>
</tr>
<tr>
<td>1NS1</td>
<td>25</td>
<td>20</td>
<td>0.09</td>
<td>ASC</td>
</tr>
<tr>
<td>2NS1</td>
<td>40</td>
<td>10</td>
<td>0.02</td>
<td>PUR</td>
</tr>
<tr>
<td>3NS1</td>
<td>50</td>
<td>10</td>
<td>0.02</td>
<td>PUR</td>
</tr>
<tr>
<td>4NS1</td>
<td>50</td>
<td>10</td>
<td>0.02</td>
<td>PUR</td>
</tr>
<tr>
<td>5NS1</td>
<td>40</td>
<td>10</td>
<td>0.10</td>
<td>ASC</td>
</tr>
<tr>
<td>6NS1</td>
<td>20</td>
<td>10</td>
<td>0.93</td>
<td>ASC</td>
</tr>
<tr>
<td>7NS1</td>
<td>0</td>
<td>10</td>
<td>0.66</td>
<td>ASC</td>
</tr>
<tr>
<td>8NS1</td>
<td>20</td>
<td>10</td>
<td>0.50</td>
<td>ASC</td>
</tr>
<tr>
<td>9NS1</td>
<td>40</td>
<td>10</td>
<td>0.15</td>
<td>ASC</td>
</tr>
<tr>
<td>10NS1</td>
<td>75</td>
<td>20</td>
<td>0.0001*</td>
<td>ASC/PUR</td>
</tr>
<tr>
<td>11NS1</td>
<td>50</td>
<td>10</td>
<td>0.04*</td>
<td>ASC</td>
</tr>
<tr>
<td>12NS1</td>
<td>10</td>
<td>10</td>
<td>0.95</td>
<td>ASC</td>
</tr>
<tr>
<td>13NS1</td>
<td>30</td>
<td>10</td>
<td>0.30</td>
<td>ASC</td>
</tr>
<tr>
<td>14NS1</td>
<td>95</td>
<td>40</td>
<td>&lt;0.0001*</td>
<td>ASC/PUR</td>
</tr>
<tr>
<td>15NS1</td>
<td>0</td>
<td>10</td>
<td>0.74</td>
<td>ASC</td>
</tr>
<tr>
<td>16NS1</td>
<td>90</td>
<td>10</td>
<td>0.0001*</td>
<td>ASC</td>
</tr>
<tr>
<td>17NS1</td>
<td>75</td>
<td>20</td>
<td>&lt;0.0001*</td>
<td>PUR</td>
</tr>
<tr>
<td>18NS1</td>
<td>10</td>
<td>10</td>
<td>0.14</td>
<td>ASC</td>
</tr>
<tr>
<td>19NS1</td>
<td>20</td>
<td>10</td>
<td>0.36</td>
<td>ASC</td>
</tr>
<tr>
<td>21NS1</td>
<td>40</td>
<td>10</td>
<td>0.27</td>
<td>ASC</td>
</tr>
<tr>
<td>22NS1</td>
<td>70</td>
<td>10</td>
<td>0.004*</td>
<td>ASC</td>
</tr>
<tr>
<td>23NS1</td>
<td>0</td>
<td>10</td>
<td>0.21</td>
<td>ASC</td>
</tr>
</tbody>
</table>

Structure of WNV NS1_{172–352} in complex with 22NS1 Fab

What can ZIKV NS1 structure tell us?

• Electrostatic potential map: affect the host interaction

• Membrane association site

• Vulnerable sites for development of diagnostic tools
Crystal structure of Zika NS1(172-352)
Diverse electrostatic potential on host-interaction interface of different flaviviruses
Full-length Zika NS1 structure
Comparison of flavivirus NS1 structures

Ladder surface

ZIKV
DENV2
WNV

Loop surface

180°

EMBO Journal. 2016
Comparison of electrostatic potential maps for different flavivirus NS1 structures
Hydrophobic protrusion for membrane interaction

A hydrophobic ‘spike’ observed in ZIKV structure
Hydrophobic “spike” can contribute to the hexamer formation
Hydrophobic “spike” can be involved in membrane association
Spike region is predicted to be involved in replication process
Zika strain MR766, the original 1947 Ugandan strain

Extended surface for membrane association in Zika virus NS1 structure

W Clay Brown¹,⁵, David L Akey¹,⁵, Jamie R Konwerski¹, Jeffrey T Tarrasch¹, Georgios Skiniotis¹,², Richard J Kuhn³,⁴ & Janet L Smith¹,²
Conserved regions of flavivirus NS1
The many functions for extracellular sNS1

Unsolved key questions

Could Zika NS1 help virus to penetrate the blood-placenta barrier, blood-brain barrier, blood-eye barrier and blood-testis barrier?

Can antiviral intervention targeting NS1 prevent the virus to infect fetus?
Acknowledgment

George F Gao
Hao Song
Jianxun Qi
Xiaoying Xu
Haiyuan Wang
Yuqian Liu
Chao Su

Thanks for your attention!