Explaining Flavivirus Congenital Neurotropism with Thermodynamics

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Benasque, July 19, 2018

Flaviviruses are a Global Health Threat

- FV include human pathogens like YFV, DENV, JEV, WNV, TBEV
- Typically transmitted by mosquitoes and ticks
- Millions of infections every year
- Broad range of clinical manifestations
  - Headache / rash / (hemorrhagic) fever / meningitis / encephalitis
- FV neurotropism reported in adults for DENV, YFV, WNV

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- 2015-2017 ZIKV outbreak in the Americas
- Congenital neurotropism
- High increase in microcephaly cases in newborns

Source: Wikipedia

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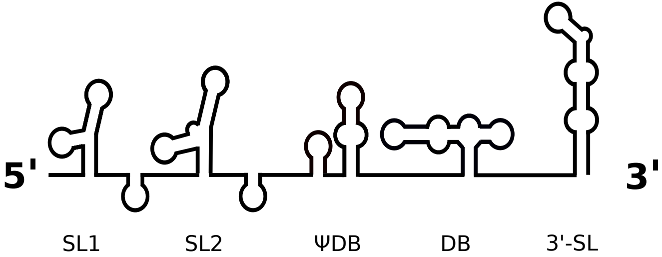
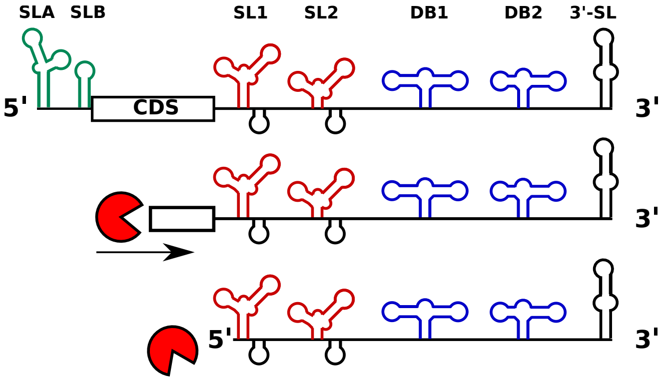
Are there other emerging FV that have a similar neurotropic potential in the developing fetus?

Flavivirus genome characteristics

- Single-stranded, positive-strand RNA viruses
- Enters cell through receptor-mediated endocytosis
- Capped, non-polyadenylated genome (gRNA) of 10-12kb length
- Encodes a single ORF, flanked by structured 5’-UTR and 3’-UTR
- Translation of FV ORF yields a single polyprotein



Flaviviruses hijack the host mRNA degradation machinery



- Accumulation of short flavivirus RNA (sfRNA) upon infection
- Stable decay intermediates produced by partial Xrn1 degradation
- Xrn1 is efficiently stalled at conserved xrRNA structures
- sfRNA modulates pathogenicity
- Many host proteins bind sfRNA

Musashi interacts with 3’UTR

Musashi (Msi) is a highly conserved family of proteins in vertebrates and invertrebrates that act as a translational regulator of target mRNA.

- Involved in cell proliferation and differentiation
- Two paralogs in mammals, Msi-1 and Msi-2
- Expressed in stem cells and overexpressed in tumors
- Two RNA-regulation domains (RRM)
- Binds single-stranded `UAG` core motif in the 3’UTR of mRNA

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THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 289, NO. 51, pp. 35530–35541, December 19, 2014

A Conserved Three-nucleotide Core Motif Defines Musashi RNA Binding Specificity*

Received for publication, July 16, 2014, and in revised form, October 20, 2014 Published, JBC Papers in Press, November 3, 2014, DOI 10.1074/jbc.M114.597112

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Mol Cell Biol 35:2965-2978 (2015)

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Does Msi interact with flavivirus 3'UTR?

Musashi is involved in ZIKV neurotropism

A recent study has shown that Msi-1 promotes ZIKV replication in glioblastoma, neuroblastoma and neuronal stem cells

Science

REPORTS

Cite as: P. L. Chavali *et al*., *Science* 10.1126/science.aam9243 (2017).

Neurodevelopmental protein Musashi 1 interacts with the Zika genome and promotes viral replication

Pavithra L. Chavali,[1*†] Lovorka Stojic,[1*] Luke W. Meredith,[2] Nimesh Joseph,[1] Michael S. Nahorski,[3] Thomas J. Sanford,[2] Trevor R. Sweeney,[2] Ben A. Krishna,[4] Myra Hosmillo,[2] Andrew E. Firth,[2] Richard Bayliss,[5] Carlo L. Marcelis,[6] Susan Lindsay,[7] Ian Goodfellow,[2] C. Geoffrey Woods,[3] Fanni Gergely[1‡]

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Another study addressed the qeustion whether related arboviruses could cause transplacental infection and fetal demise

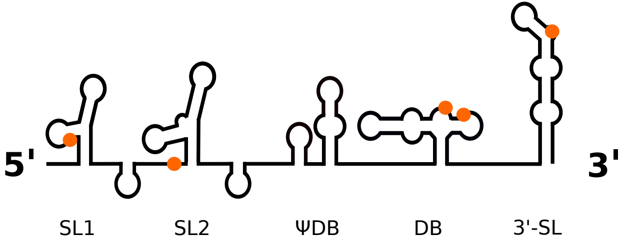
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

EMERGING INFECTIONS

Zika virus–related neurotropic flaviviruses infect human placental explants and cause fetal demise in mice

Derek J. Platt,[1*] Amber M. Smith,[2*] Nitin Arora,[3,4] Michael S. Diamond,[1,2,5,6] Carolyn B. Coyne,[3,4] Jonathan J. Miner[1,2,5†]

ZIKV 3'UTR revisited



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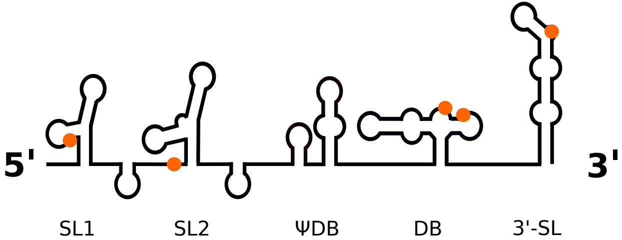

$$Z = \sum_{s} e^{-E(s)/RT}$$

$$\Delta G_{\mathrm{open}} = -RT \ln P(\mathrm{unpaired})$$

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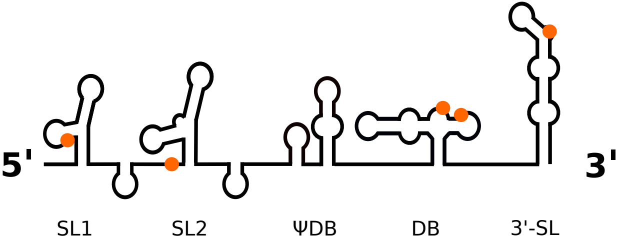

$$Z = \sum_s e^{-E(s)/RT}$$

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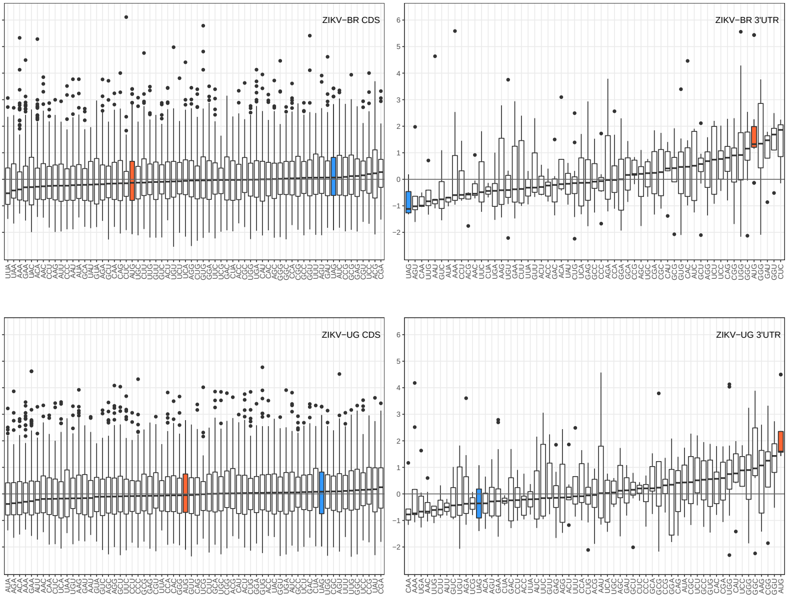
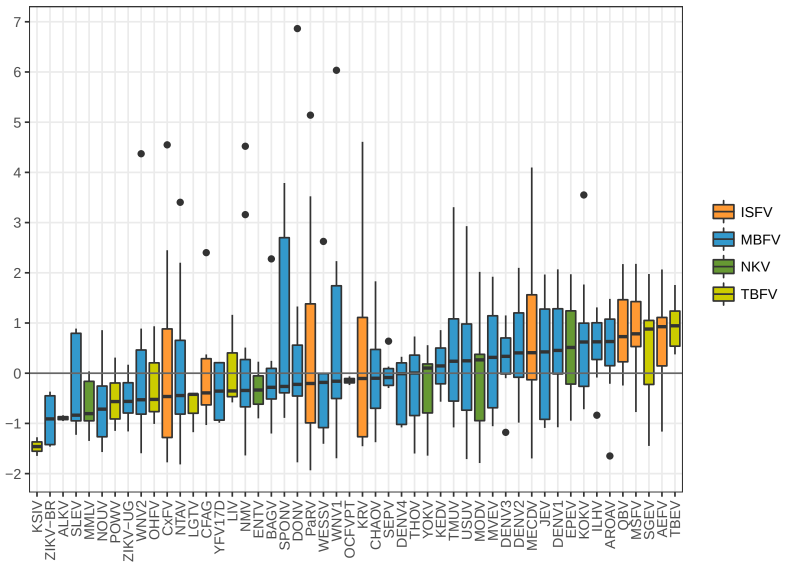
We use `RNAplfold` to compute the opening energy of trinucleotide x in a genomic (± 100 nt) as well as a shuffled sequence context and compute a z score statistics.

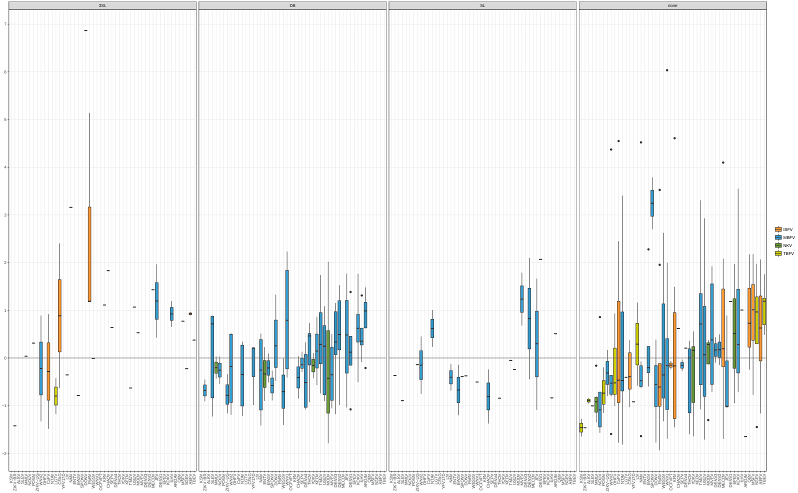
Trinucleotide opening energies in ZIKV



MBE opening energies in related viruses

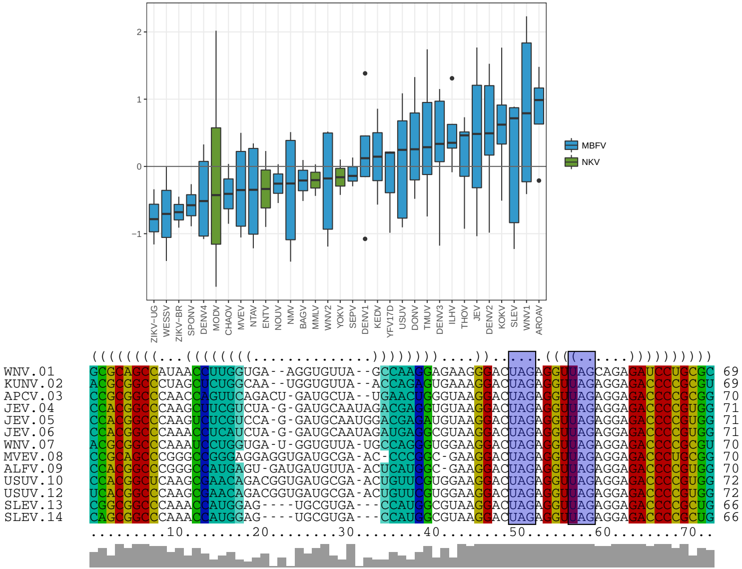


MBEs opening energies by xrRNA

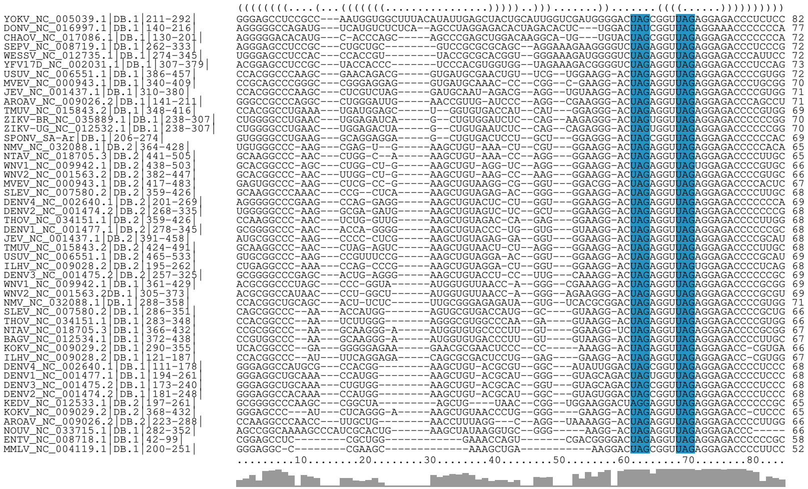


MBEs accumulate within dumbbell (DB) elements in MBFV and NKV

MBE in MBFV and NKV DB elements



Structure and sequence conservation in DB elements



- Highly conserved MBE pair in DB elements
- Central multiloop and distal hairpin loop

- Our biophysical model corroborates experimental findings of Msi involvement in ZIKV replication
- MBEs in flavivirus DB elements show primary sequence conservation
- ZIKV might not be alone in its capacity to cause severe neuropathology in the developing fetus
- A possible role of Msi in the replication cycle of some FV?

Acknowledgments

Collaborator
Adriano De Bernardi Schneider
(UNC Charlotte)

TBI Vienna
Ivo L. Hofacker
Roman Ochsenreiter
Andrea Tanzer

FWF
Der Wissenschaftsfonds.

SFB RNA regulation of the transcriptome (FWF-F43)

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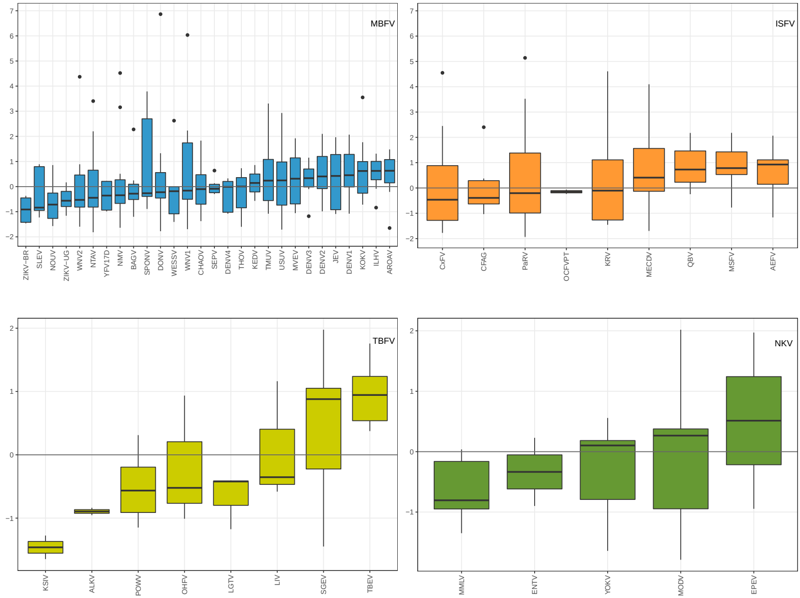
Thank you!

MBE opening energies in related viruses



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