

Structured Regions in Flaviviridae

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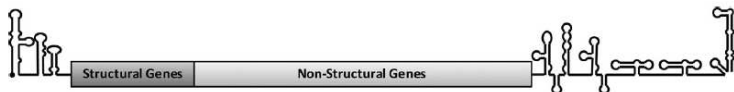
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Bled, Feb 16, 2016

Flavivirus characteristics

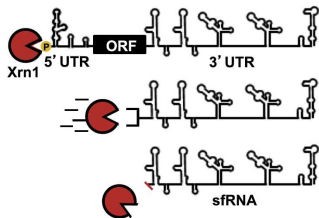
- ▶ (+) ssRNA viruses
- ▶ Enters cell through receptor-mediated endocytosis
- ▶ Capped, non-polyadenylated genome (gRNA) of 10-12kb length
- ▶ Encodes a single ORF, flanked by structured 5'-UTR and 3'-UTR
- ▶ Translation of FV ORF yields a single polyprotein
- ▶ RNA structure elements in 3' UTRs (xrRNAs)
- ▶ sub-genomic noncoding RNAs (sfRNAs)



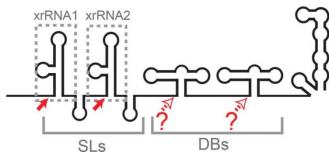
sfRNA is generated upon incomplete gRNA degradation

Upon infection, FV hijack the the host cell's RNA turnover machinery

- ▶ decapping of mRNA \rightarrow 5' monophosphate as substrate for Xrn1
- ▶ Exoribonuclease Xrn1 degrades ss-5'p RNA in a 5' \rightarrow 3' direction
- ▶ Xrn1 stalls near the beginning of FV 3'UTR



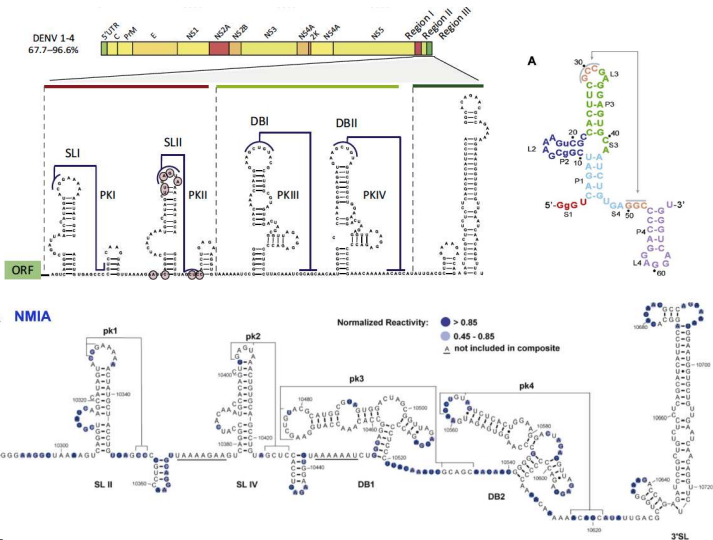
Stalling in **Xrn1-resistant RNAs (xrRNAs)** \rightarrow leaving **intact sfRNA**



Chapman et al., 2014

sfRNA structural elements

The mechanism of Xrn1 stalling has been extensively studied in DENV, WNV and MVEV. Tertiary interactions are crucial for Xrn1 stalling.



2015/2016 Zika outbreak Central and South America

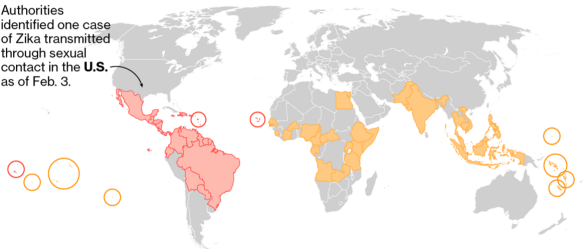
An explosive pandemic of **Zika virus (ZIKV) infection** is reported throughout Central and South America and the Caribbean.

Zika's Past and Present

■ Active transmission (as of Feb. 3, 2016)

■ Evidence of previous presence*

Authorities identified one case of Zika transmitted through sexual contact in the **U.S.** as of Feb. 3.



*Includes locally-acquired cases, isolated virus and evidence of exposure to Zika in blood samples.

SOURCES: Centers for Disease Control and Prevention, Pan American Health Org.

Bloomberg

Originally isolated in 1947 (Uganda), Zika outbreaks were reported in 2007 (Micronesia), 2010 (Cambodia), 2013 (French Polynesia) and 2014 (Haiti).

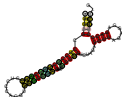
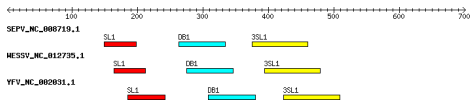
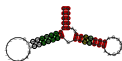
Zika as a Global Health Threat

Health authorities in Brazil have observed an **increase in Guillain-Barré syndrome** which coincided with Zika virus infections and an **increase in babies born with microcephaly**.

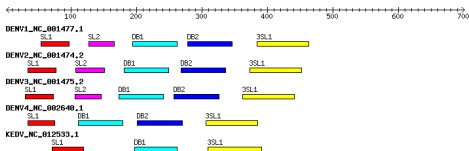
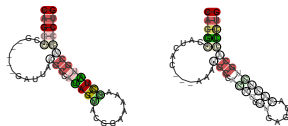
The possible relationship between microcephaly in babies and Zika virus is currently investigated, as well as other potential causes.



Single copy - Yellow fever virus group (YFVG)



Duplicate SL/DB: Dengue Virus Group (DENVG)

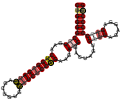
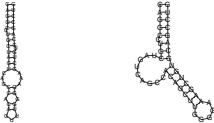
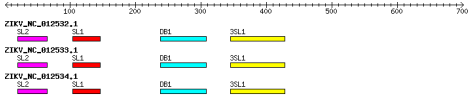


Duplicate SL/DB: Spondweni Virus Group (SPOVG)

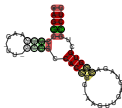
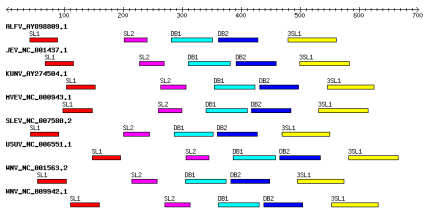


Uganda

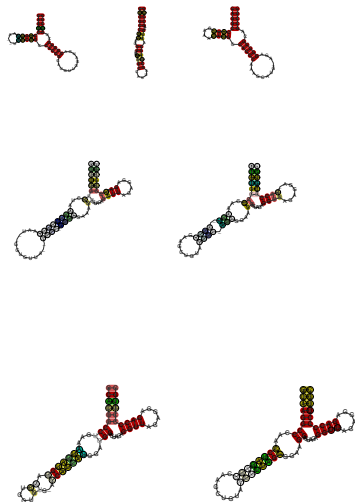
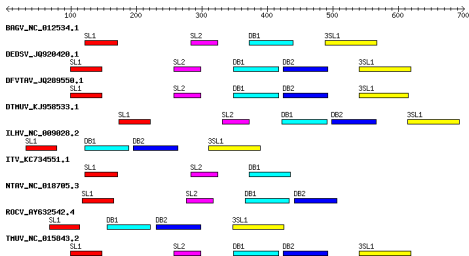
Brazil



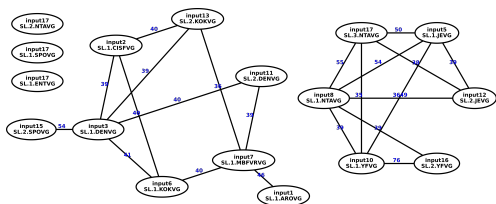
Duplicate SL/DB: Japan encephalitis Virus Group



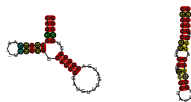
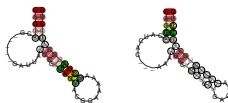
Duplicate SL/DB: Ntaya Virus Group



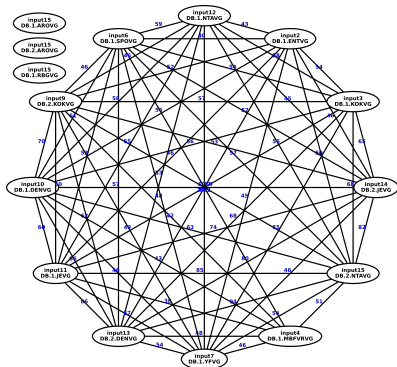
Comparison SL Elements



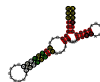
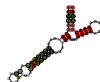
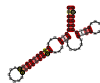
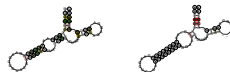
→ two groups:
 YFVG/NTAVG/JEVG
 DENVG/SPOVG/KOKV/AROVG



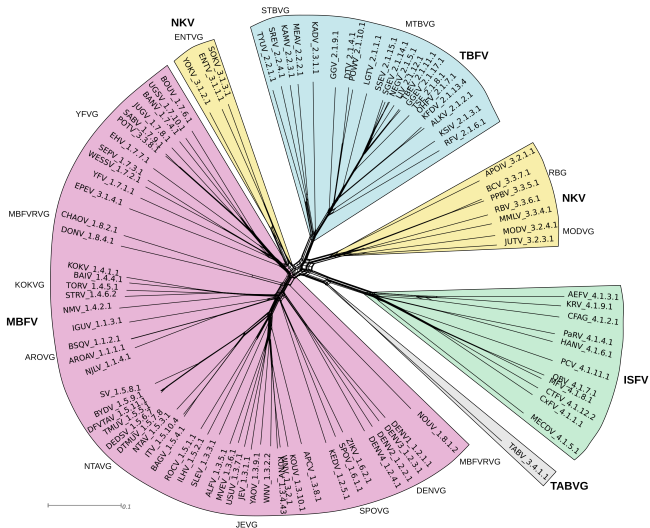
Comparison of DB elements



→ DB elements form one group



3UTR annotation status quo



TBEV: Tick-borne (239/170)
MBFV: Mosquito-borne
(6,900/6,391)
ISFV: Insect-specific (53/3)
NKV: no known vector (27/12)

**total: 7,212 genomes
(Genbank 11/2016)
16,797 SL/DB/SSL elements in
6,576 genomes**

Summary

- ▶ DB and SL elements crucial for sfRNA production
- ▶ sfRNAs block innate immune response of host → virus replication
- ▶ Mosquito-borne FV underwent duplication of SL & DB
- ▶ specific SL elements in individual virus groups → sub-functionalization?
- ▶ Asian/American Zika strains: mutations in SL elements → more stable SL structures
- ▶ evidence for link pathogenicity ↔ RNA structure elements

Acknowledgments

Team:

Andrea Tanzer
Michael Wolfinger
Roman Ochsenreiter
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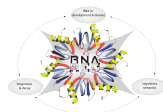


DK RNA Biology (FWF-W 1207)

FWF

Der Wissenschaftsfonds.

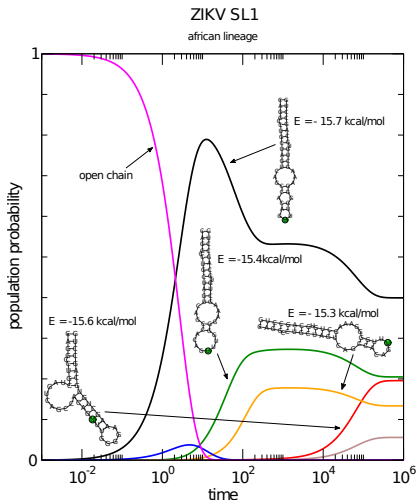
'RNALands' (I-1804-N28 and
ANR-14-CE34-0011)
'mRNAs von Viren: Evolution und
Struktur-Funktionsbeziehungen'
(I-1303)



SFB RNA regulation of the
transcriptome (FWF-F43)

Thank you!

Kinetic folding behaviour of SL1 elements



ZIKA SL1 - African lineage
Uganda, NC_012532.1
(funct: red trajectory)

- ▶ appears late in simulation
- ▶ high E-barrier to MFE structure
- ▶ low population density in equilibrium

Kinetic folding behaviour of SL1 elements

ZIKA SL1 - Asian lineage
Brazil, KU365777.1
(funct: black & red trajectories)

- ▶ multiple functional structures with low refolding E-barrier
- ▶ present early on
- ▶ dominate equilibrium

