

Rewriting the history of Zika sfRNA evolution

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2015 Zika virus outbreak in Central and South America

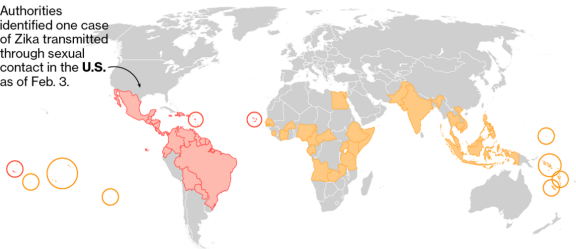
An explosive pandemic of **Zika virus (ZIKV) infection** is reported throughout Central and South America and the Caribbean.

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).

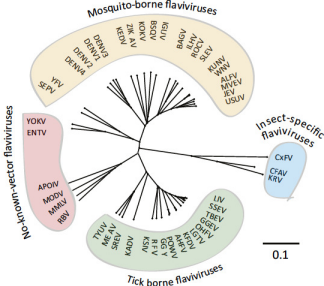
Zika as a Global Health Threat

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.



Flavivirus classification

Zika virus is a member of the Spondweni serocomplex within the **genus *Flavivirus*** (FV), **family *Flaviviridae*** and maintained in a sylvatic transmission cycle involving non-human primates and mosquitoes from the *Aedes* genus (mainly *Aedes aegypti* in tropical regions). Humans serve as identical hosts.

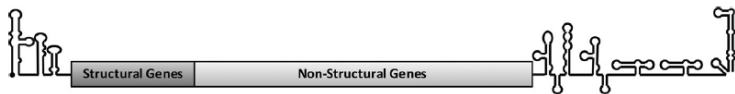


FV ecological groups

- Mosquito-bourne (MBFV)
- Tick-bourne (TBFV)
- Vertebrate-specific, no known vector (NKFV)
- Insect-speficic (ISFV)

Flavivirus characteristics

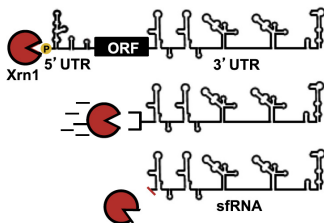
- Single-stranded, positive-strand RNA viruses
- Enters cell through receptor-mediated endocytosis
- Capped, non-polyadenylated genome (gRNA) of 10-12kb length
- Encodes a single ORF, flanked by structured 5'-UTR and 3'-UTR
- Translation of FV ORF yields a single polyprotein



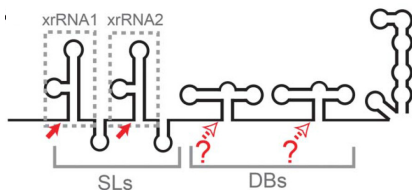
sfRNA is generated upon incomplete gRNA degradation

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

- mRNAs destined for degradation are decapped, leaving a 5' monophosphate as substrate for Xrn1
- Exoribonuclease Xrn1 degrades ss-5'p RNA in a 5'→3' direction
- Xrn1 stalls near the beginning of FV 3'UTR

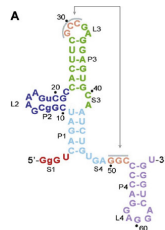
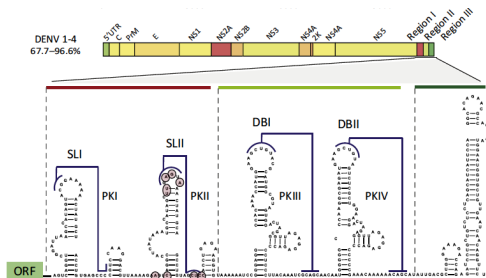


Stalling occurs at **Xrn1-resistant RNAs (xrRNAs)**, leaving **intact sfRNA**

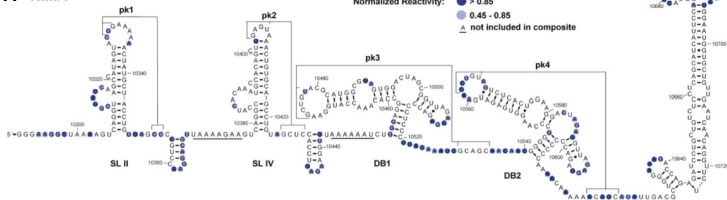


sfRNA structural elements

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

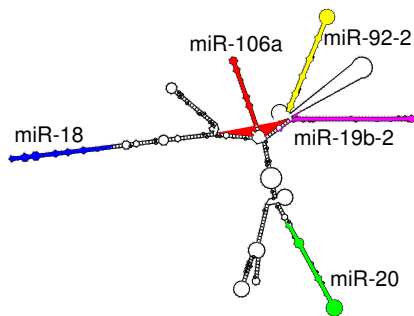


A NMIA

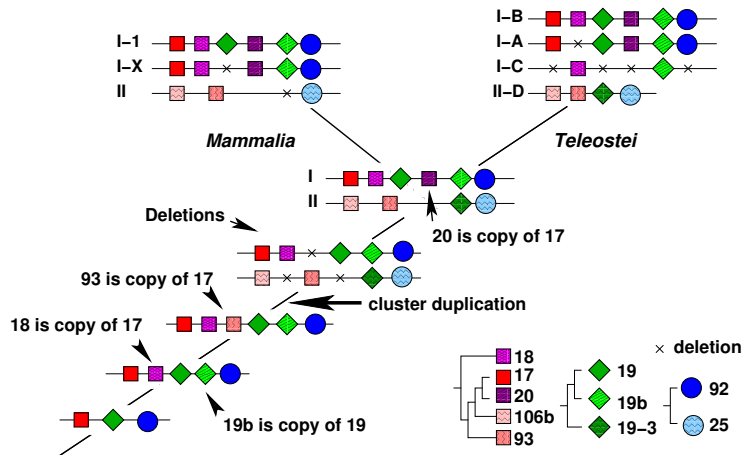


micro RNA clusters

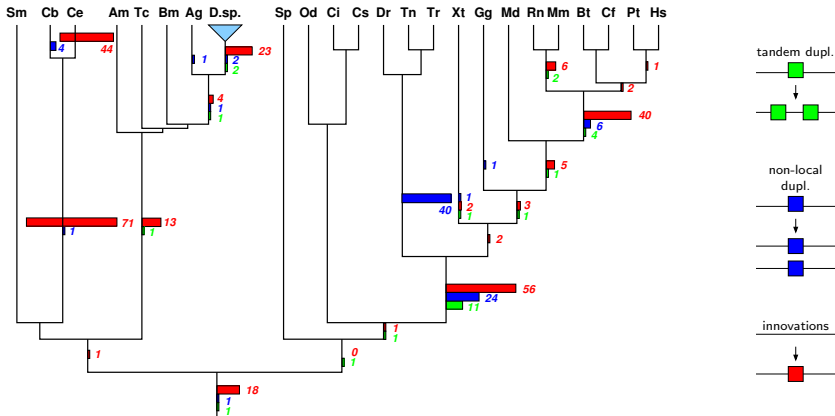
- primary-precursor micro RNA (pri-miRNA) of cluster
- Cleavage I: Drosha
- precursor miRNA (pre-miRNAs)
- Cleavage II: Dicer
- mature miRNA (miRNAs)
- post-transcriptional gene silencing (PTGS)
- mRNA degradation (RNAi)
- translational repression



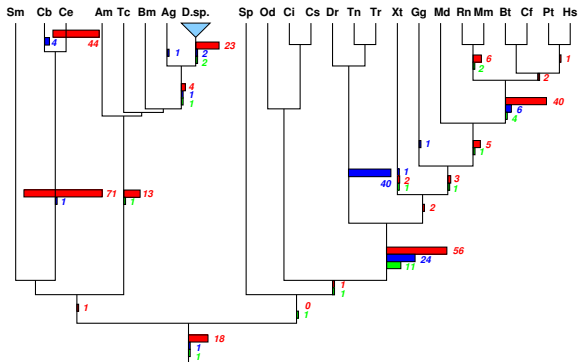
Mir-17 cluster evolution



Expansion of The Metazoan MicroRNA Repertoire

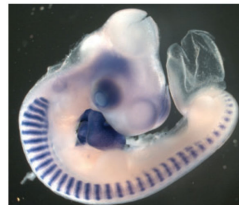


MicroRNAs in Development

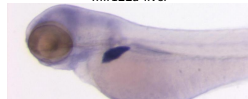


Hertel *et al.*, BMC Genomics.2006;7:25

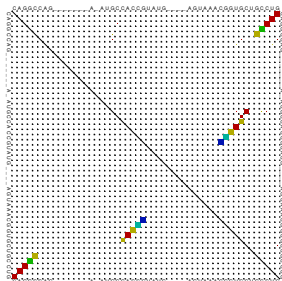
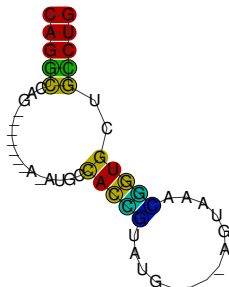
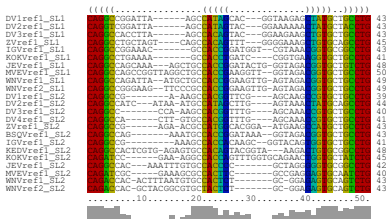
chicken stage 22
mir1, heart and somites



zebrafish
mir122a liver



RNA structure of SL elements



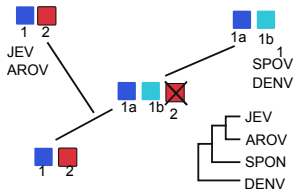
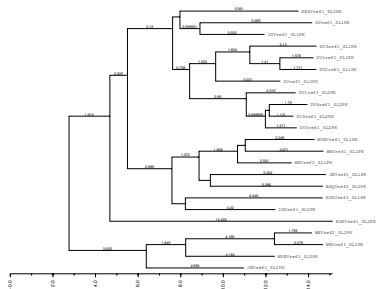
- 40 nt in length
- 1-2 copies per virus species
- conserved structure
- MFE structure not functional

Phylogenetic reconstruction

$$z(I, J) = \frac{s(I, J) - m}{\sqrt{v}} \quad (1)$$

- zscore of pairwise alignments as distance measure
- two sequences I and J
- identity score $s(I, J)$ of pairwise alignment
- random permutation of positions of I and J independently of each other results in sequences I_π and J_π
- mean score m and the variance v are estimated from a sample of 1000 alignments of sequences I_π and J_π
- z-score used as similarity measure of I and J for WPGMA clustering

Duplication history of SL elements



Summary and outlook

- 3UTR contains 3 structure families
- SL elements arose through independent deletions and tandem duplications
- functional structures not most stable
- → build covariance model for SL
- → search flaviviridae
- → extend to DB elements
- → model folding kinetics
- ⇒ apply on detailed analysis of zika strains

Team

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Thank you!