Impact of genomic RNA structure and non-coding RNAs in Zika virus neuropathogenesis

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Zika Virus (ZIKV) infection has been neglected during the first 60 years after its discovery. In the last years the unexpected rapid spread and potential ability to cause congenital syndrome have made ZIKV a Public Health Emergency of International Concern. ZIKV genome has two flanking UTR regions and a single long open reading frame encoding a polyprotein. In other Flavivirus, the 3'UTR sequence form particular RNA structures, which are important for virus biology and lifecycle. It is unclear, however, if variations in these viral secondary structures may also contribute to the neuropathogenesis induced by Zika infection. In this work, we developed and applied an automated pipeline called StructRNAfinder on 55 publicly available 3'UTR sequences from ZIKV and other 32 related flaviviruses. Our tool provides an easy-to-use method to functionally annotate RNA structures nucleotide sequences (DNA or RNA). The same set of sequences was also submitted to analysis on PPfold software, in order to find the differences in terms of pairing composition and general topology of ZIKV 3'UTRs. Our analysis found a group of 47 ZIKV exclusive RNA families; and other 25 families available exclusively on other flaviviruses. The results revealed differences in terms of secondary structure composition along this region in different ZIKV isolates,and was able to group the sequences between Asian/American and African lineages. The PPfold analysis also illustrated clear differences between these two lineages, revealing that African lineage seems to be much more structured than the Asian lineage. These structural ZIKV RNAs, as well as the topology of the 3'UTR region, may have critical roles in virus biology, and can be directly related to human neurological disorders.

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