Combatting Zika Virus through Enhancing RNAi

The outbreak and rapid spread of Zika virus (ZIKV) in the Western Hemisphere has imposed a global public health threat since 2015.

ZIKV is a positive-sense single-stranded RNA virus (where the 'positive-sense' means that the viral RNA can be directly translated by the host cell into viral proteins) that belongs to the genus Flavivirus in the family Flaviviridae. ZIKV preferentially infects and targets human neural progenitor cells (hNPCs) – cells that later give rise to the building blocks of human cortex – and causes fetal microcephaly – an abnormally small head and underdeveloped brain of newborns upon maternal infection. Indeed, hNPCs play vital roles throughout life, whose dysfunction could lead to severe brain disorders. Yet how hNPCs fight back against ZIKV invasion remains poorly understood.

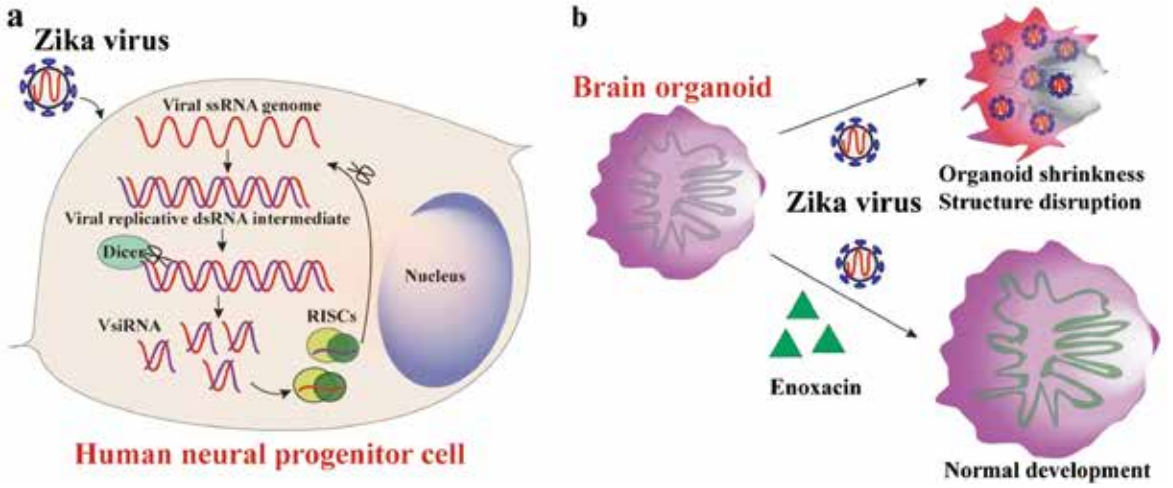
Not long ago, the circumstance changed. RNA interference (RNAi) response in hNPCs was found to play critical roles in defending against ZIKV infection at the early stage of human brain development. This finding was made by a joint team, led by Prof. ZHOU Xi from the CAS Wuhan Institute of Virology, Prof. HU Baoyang from the CAS Institute of Zoology, and Prof. QIN Chengfeng from Beijing Institute of Microbiology and Epidemiology of the Academy of Military Medical Sciences. The research paper has been published as the cover story in *Cell Research* (April 2019).

RNAi is an evolutionarily conserved gene silencing mechanism that acts to destroy RNA molecules in nuclear-bearing cells, which could also act as an innate antiviral immune mechanism when acting to destroy viral RNAs. However, the importance of RNAi as a mammalian antiviral defense mechanism had been questioned due to the absence of virus-derived small interfering RNAs (vsiRNAs) in mammalian cells infected with wild-type human viruses until not long ago.

Recently, Chinese scientists directly detected that ZIKV infection triggers abundant production of vsiRNAs in hNPCs. They proved that the RNAi machinery in hNPCs was spurred to cleave the double-stranded RNAs formed during ZIKV genome replication, resulting in the production of abundant vsiRNAs. They also showed that the disruption of the RNAi pathway by knocking down Dicer or AGO2, the two essential RNAi machinery components, enhanced ZIKV replication in hNPCs.

The cover image illustrates how RNAi (terracotta warrior from the Qin dynasty of China), as an "ancient" antiviral immunity mechanism, protects human neural progenitors (the wall) and brain organoids (beacon tower) from the invasion of Zika viruses. In antiviral RNAi, Dicer (the crossbow) produces viral siRNAs (the arrows) from viral dsRNA to specifically target and cleave viral genomic RNAs. (Credit: ZHOU Xi, CAS and QIN Chengfeng, AMMS).

Furthermore, they also showed that a well-known RNAi enhancer, enoxacin, exerts anti-ZIKV activity in hNPCs and brain organoids, and enoxacin treatment



RNAi plays antiviral roles in ZIKV-infected hNPCs (a); RNAi enhancer, enoxacin, exerts anti-ZIKV activity in brain organoids (b). (Credit: SHI Pei-yong, UTMB)

could completely prevent ZIKV-induced microcephalic phenotypes in brain organoids.

Based on these converging evidences, they concluded that the evolutionarily ancient antiviral mechanism, RNAi, serves as an active antiviral immune defense in hNPCs against ZIKV viral infection. This study also opens a new window to therapeutically inhibit ZIKV replication and pathogenesis in hNPCs by enhancing RNAi. The demonstrated efficacy of enoxacin, a potent RNAi enhancer, on defending ZIKV infection in hNPCs and brain organoids warrants further investigation. It is also worth to look for compounds with higher RNAi-enhancing activity, and expand this proof-of-concept antiviral strategy to fight against other types of congenital viral infection that can also be stopped by RNAi.

(By YAN Fusheng)

Reference

Yan-Peng Xu *et al*., Zika Virus Infection Induces RNAi-Mediated Antiviral Immunity in Human Neural Progenitors and Brain Organoids. *Cell Research* 29, 265-273 (Published: April 01, 2019). doi: 10.1038/s41422-019-0152-9.