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VIRAL EVOLUTION

Zika is on point to increase spread

Zika virus is a flavivirus that is transmitted by *Aedes* spp. mosquitoes. Phylogenetic studies have revealed that the virus has evolved into two lineages, the African and Asian lineages. In the past, both lineages only sporadically caused infections in humans, until the recent outbreaks in French Polynesia (2013–2014) and South America (2015–2016), which were caused by Zika virus strains that belong to the Asian lineage. However, the underlying mechanisms that caused the rapid spread of the virus during the recent outbreaks are unclear. In this study, Liu, Liu, Du, Shan *et al.* showed that a mutation in non-structural protein 1 (NS1) enhanced the infectivity of viruses that belong to the Asian lineage in their mosquito vectors, and suggested that this might have contributed to the increased prevalence and spread of the virus from Asia to the Americas.

> “a mutation in non-structural protein 1 (NS1) enhanced the infectivity”

The authors used a host–mosquito acquisition model to compare the infectivity of two clinical Zika virus strains that belong to the Asian lineage (FSS13025 and GZ01, which were isolated in 2010 and 2016, respectively), and found that mice that were infected with the GZ01 strain exhibited higher levels of NS1 in the blood. Subsequently, these mice were subjected to daily biting by mosquitoes and the infection prevalence was substantially higher in mosquitos that fed on mice that were infected with the GZ01 strain than mosquitos that fed on animals infected with the FSS13025 strain. This finding suggests that the presence of viral antigens in the blood of viraemic mammalian hosts (NS1 antigenaemia) might be responsible for the difference in mosquito infectivity between the GZ01 and FSS13025 strains. Indeed, neutralization of NS1 by treatment with antibodies decreased the prevalence of infections of mosquitoes by the GZ01 strain, whereas the presence of ectopically expressed NS1 enhanced the infectivity of the FSS13025 strain.

Next, sequence analysis revealed that NS1 of GZ01 contains an alanine-to-valine amino acid substitution at residue 188. Moreover, Zika virus isolates collected from the Asia lineage before 2012 had an alanine at position 188 of NS1, whereas all isolates of the Asian lineage collected after 2013 had the mutation to valine at this position, which suggests that the amino acid substitution might have contributed to the recent epidemics. In agreement with this, mutating residue 188 in the FSS13025 strain from alanine-to-valine substantially increased the secretion of NS1 in supernatants of infected cells, as well as in the blood of infected mice. Moreover, the amino acid substitution enhanced the transmission of Zika virus from mice to mosquitoes in the mutant compared with the wild type, whereas the prevalence of the mutant virus in mosquitoes was decreased in the presence of neutralizing NS1 antibodies. The data suggest that the valine residue at residue 188 of NS1 has a crucial role in antigenaemia, which is essential for the transmission of Zika virus from mammalian hosts to mosquitoes.

In summary, this study provides a potential explanation for the recent re-emergence of Zika virus.

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ORIGINAL ARTICLE Liu, Y., Liu, J., Du, S., Shan, C. *et al.* Evolutionary enhancement of Zika virus infectivity in *Aedes aegypti* mosquitoes. *Nature* http://dx.doi.org/10.1038/nature22365 (2017)