Report

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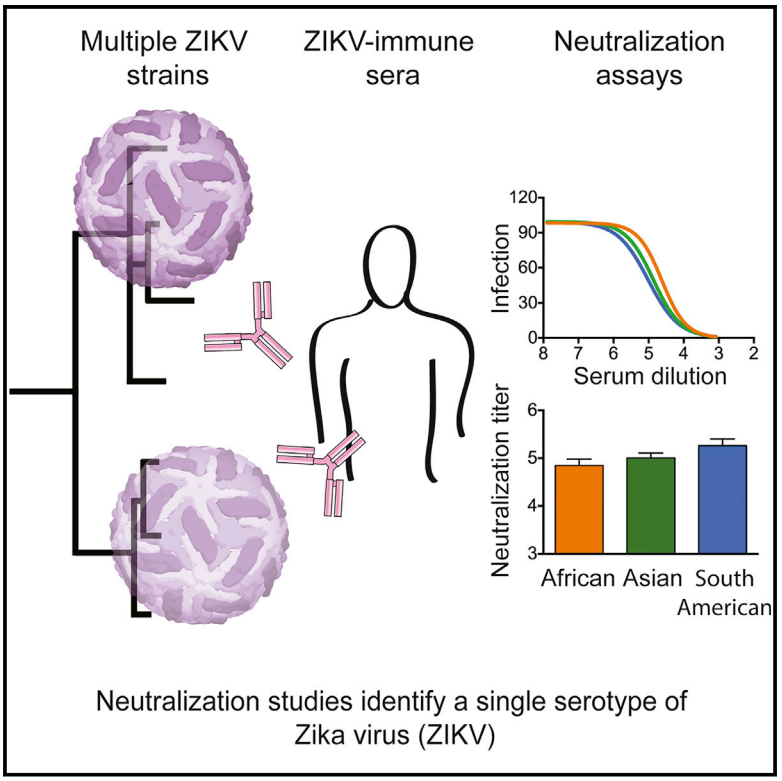
Broadly Neutralizing Activity of Zika Virus-Immune Sera Identifies a Single Viral Serotype

Graphical Abstract



Neutralization studies identify a single serotype of Zika virus (ZIKV)

Highlights

- Neutralization studies with convalescent ZIKV-immune sera identify a single serotype
- Infection with a single ZIKV strain elicits broadly neutralizing antibodies
- Strain selection may not be a critical parameter for ZIKV vaccine development

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In Brief

Dowd et al. investigate the breadth of the neutralizing antibody response to ZIKV. They demonstrate that contemporary South American, Asian, and early African ZIKV strains are similarly sensitive to neutralization by ZIKV-confirmed convalescent human serum.

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Broadly Neutralizing Activity of Zika Virus-Immune Sera Identifies a Single Viral Serotype

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SUMMARY

Recent epidemics of Zika virus (ZIKV) have been associated with congenital malformation during pregnancy and Guillain-Barré syndrome. There are two ZIKV lineages (African and Asian) that share >95% amino acid identity. Little is known regarding the ability of neutralizing antibodies elicited against one lineage to protect against the other. We investigated the breadth of the neutralizing antibody response following ZIKV infection by measuring the sensitivity of six ZIKV strains to neutralization by ZIKV-confirmed convalescent human serum or plasma samples. Contemporary Asian and early African ZIKV strains were similarly sensitive to neutralization regardless of the cellular source of virus. Furthermore, mouse immune serum generated after infection with African or Asian ZIKV strains was capable of neutralizing homologous and heterologous ZIKV strains equivalently. Because our study only defines a single ZIKV serotype, vaccine candidates eliciting robust neutralizing antibody responses should inhibit infection of both ZIKV lineages, including strains circulating in the Americas.

INTRODUCTION

Zika virus (ZIKV) is a mosquito-transmitted flavivirus that has emerged from relative obscurity to cause an epidemic of great public health concern. During the half-century that followed its discovery, ZIKV was rarely linked to disease in humans, despite considerable transmission (Dick, 1953; Petersen et al., 2016). The emergence of epidemic ZIKV was first reported in Yap island in 2007, followed by outbreaks in French Polynesia in 2013 and 2014 and regularly thereafter in other islands of the Pacific. ZIKV was introduced into the western hemisphere in 2014–2015 and spread rapidly to 40 or more countries and territories. Historically, symptomatic ZIKV infection of humans was described as a self-limiting mild febrile illness associated with rash, arthralgia, and conjunctivitis (Petersen et al., 2016). However, recent ZIKV infections also have been associated with neurological complications, including Guillain-Barré syndrome and meningoencephalitis (Brasil et al., 2016a, 2016b; Cao-Lormeau et al., 2016; Oehler et al., 2014). Of greatest concern, ZIKV infection is now linked causally to microcephaly and intrauterine growth retardation in the fetuses of women infected with the virus while pregnant (Hazin et al., 2016).

Flaviviruses are spherical virus particles that incorporate two structural proteins, premembrane/membrane (prM/M) and envelope (E), into their lipid envelope. High-resolution structures of the mature ZIKV virion and ectodomain of the E protein have been solved (Dai et al., 2016; Kostyuchenko et al., 2016; Sirohi et al., 2016). Similar to other flaviviruses, mature ZIKV virions are relatively smooth particles that incorporate 180 copies each of the E and M proteins. Neutralizing antibodies play a critical role in protection against flaviviruses and bind epitopes located in all three E protein structural domains (Heinz and Stiasny, 2012). Additionally, potently neutralizing flavivirus antibodies have been isolated that bind surfaces composed of more than one domain or E protein (Screaton et al., 2015). Because neutralizing antibody titers correlate with protection by licensed vaccines for Japanese encephalitis virus (JEV), yellow fever virus (YFV), and tick-borne encephalitis virus (TBEV) (Belmusto-Worn et al., 2005; Heinz et al., 2007; Mason et al., 1973; Monath et al., 2002), eliciting neutralizing antibodies is a desired feature of candidate vaccines for related flaviviruses, including ZIKV.

Flaviviruses circulate as genetically distinct genotypes or lineages. ZIKV strains have been grouped into two lineages, African and Asian, which differ by <5% at the amino-acid level, including within the E protein gene (Haddow et al., 2012). The African lineage includes the historical MR-766 strain originally identified in 1947, whereas virus strains from the Asian lineage have been implicated in the recent outbreaks in Yap, French Polynesia, and the Americas. Understanding how sequence variation among ZIKV strains impacts antibody recognition is of particular importance to vaccine development. DENV, for example, circulates as four distinct serotypes that differ by 25%–40% at the