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Commentary

ZIKV Strains' Different Phenotypes in Human Neural Cells Could be a Hint for the Emergence of the New Clinical Neurological Outcomes

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Zika virus (ZIKV), the mosquito-borne flavivirus responsible for the current outbreak in Latin America, was first isolated in 1947. Nevertheless, the link between ZIKV and the neurological complications observed in humans, like Guillain-Barré syndrome (GBS) and microcephaly, was not formally established until April 2016 by the Centers for Disease Control and Prevention (CDC). Although retrospective studies have also confirmed the link in a previous outbreak in French Polynesia (2013), how these clinical signs could have gone unnoticed for almost 70 years while the virus had been circulating in Africa and Asia is surprising. The existing isolates of ZIKV have been classified in two main lineages, African and Asian, although a recent report has identified a third one, where the original African lineage was renamed to African-I, and a previously neglected lineage circulating in Senegal and Cote d'Ivoire has been named African-II (Gong et al., 2016). The Asian lineage was the one that spread to Oceania's islands and the Americas, and two main hypotheses have been proposed for the unexpected clinical outcome of ZIKV in the last outbreaks. On one hand, clinical signs could have been overlooked due to poor surveillance in low-income territories. The other possibility would be that the new derived strains would have genetically changed enough to differ in their pathogenesis (Panchaud et al., 2016).

Reports on ZIKV have been scarce for many years, until a Public Health Emergency of International Concern (PHEIC) was issued by the World Health organization (WHO) in February 2016, engaging the scientific community in an unprecedented effort to develop a coordinated global response. Although both Asian and African ZIKV strains have been shown to be neurovirulent (Barzon et al., 2016), the only African strain used for those studies (MR-766, 1947) has been extensively passaged in suckling mice brains (Haddow et al., 2012). This may have added multiple mutations that could affect the observed results, especially considering ZIKV is an RNA virus. Hence, there is still a need to clarify if the newly-found clinical manifestations are specific for the Asian lineage, or could have also been induced by the African ZIKV.

In this issue of *EBioMedicine*, Simonin et al. (2016) compare the infectivity of two low-passage isolates of ZIKV, one Asian (AS ZIKV) from French Polynesia (PF-13, 2013) and one African (AF ZIKV) from Central African Republic (ArB41644, 1989), highly homologous to strains from the African lineage-I. They observe that the AF ZIKV strain presents higher levels of infectivity and virus production than the AS ZIKV strain in human pluripotent stem cell-derived neural stem cells (iPS-derived NSCs) and in astrocytes. These results contradict a previous report on human neuro-precursor cells (NPCs), where lower replication was observed for the AF ZIKV strain compared to an AS ZIKV one; nevertheless, the African strain MR-766 was used for the infections in that study (Cugola et al., 2016). Additionally, Simonin et al. found a stronger halt in cell division, together with higher levels of induction of apoptosis when the NSCs were infected with the AF ZIKV strain compared to the AS ZIKV strain. High levels of cell death were reported before in NPCs and brain organoids infected with the MR-766 strain (Qian et al., 2016; Tang et al., 2016), but it is still unclear how this strain compares to the AS and AF ones. Simonin et al. also observed an increase in the expression of several antiviral genes upon infection of AF ZIKV (RIG-I, MDA5, TLR3 and IFN-β) that was not induced by the AS ZIKV strain. This lack of antiviral gene-modulation by the AS ZIKV strain agrees with what has been previously observed in NPCs (Hanners et al., 2016). Together, these results could point to viral persistence of AS ZIKV in the infected neural tissues by establishing a reservoir due to a lack of strong immune response in that tissue, which could explain the detection of ZIKV in neonates that were more likely infected early during pregnancy (de Araujo et al., 2016).

These interesting data would support the hypothesis of the change in phenotype from the African to the Asian lineage, provided that this study is further confirmed using additional primary isolates for a whole comparison. An effort in obtaining all the complete sequences of the isolated strains will be essential to determine the differences between ZIKV strains that could lead to a change in virulence, which could be tested by the use of reverse genetics. Additionally, differences in survival and vertical transmission rates could be analyzed using the available mouse models. Lastly, it would be important to increase the surveillance and traceability efforts of infectious cases, as the possibility exists that more ZIKV outbreaks could remain undiscovered in Africa.

In sum, Simonin et al. have contributed with this work to the research on the newly-found clinical manifestations in Asia and America showing how two strains can have different phenotypes when infecting neural cells. The confirmation that these phenotypes are respectively

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maintained both in the African and Asian ZIKV lineages will be essential to decipher the determinant factors responsible for the current ZIKV's pathology. Ultimately, understanding the mechanistic pathways underlying the respective clinical outcomes will help to effectively control the current outbreak.

Conflicts of Interest

None.

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