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Commentary

Finding Clues for Congenital Zika Syndrome: Zika Virus Selective Infection of Immature Neurons

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Since the World Health Organization (WHO) declared a Public Health Emergency of International Concern (PHEIC) in February 2016, due to the suspicion of a link between Zika virus (ZIKV) infection and fetal malformations, there has been an increasing effort by the scientific community to unravel the mechanism of infection and link to the neurological complications.

ZIKV, a mosquito-transmitted virus from the *Flaviviridae* family, was first identified in Uganda in 1947 from a sentinel rhesus monkey. It was not until 2007 when the virus was reported outside Africa and Asia, causing outbreaks in Micronesia, French Polynesia, and more recently in South, Central and North America. Apart from the natural route of transmission, through the *Aedes* sp. mosquitoes' bites, ZIKV has been shown to be transmitted by blood transfusion, vertical transmission and also through semen by sexual transmission (and more recently from female to male).

ZIKV is asymptomatic in the majority of infected people (around 80%), but in symptomatic infections it can cause mild symptoms like fever, headache, red eyes, rash, fatigue, muscle and joint pain. A small percentage of infected adults might also develop Guillain-Barré Syndrome, a rare autoimmune disorder that causes muscle weakness and, very rarely, paralysis or death. Nevertheless, the main concern is the induction of microcephaly and other severe brain malformations by ZIKV in fetuses and newborn babies from pregnant mothers that have been infected mainly during the first and second trimesters of gestation. The link between ZIKV and these neural complications was finally confirmed in April 2016 by the Centers for Disease Control and Prevention (CDC) after careful review of existing evidence, taking into account the sum of reports on detection of viral nucleic acids in fetus, premature death and abnormal growth of infected neural stem cells, and epidemiological studies from Brazil and French Polynesia among others (Rasmussen et al., 2016). However, there are still many unknown factors about the risk of development of fetal malformations and ZIKV infection in the mother, such as what is the viral load needed for the virus to be able to cross the placenta, could this step be facilitated by an specific genetic factor (*i.e.* a specific Fc receptor), does the mother need to have symptoms in order to transmit the infection to the fetus, and why can the virus easily access and infect the fetus brain whereas it does not seem to affect the mother's?

To help to address this last question, in this issue of EBioMedicine Hughes et al. compare ZIKV permissiveness of immature *versus* mature human neuronal cell lines (Hughes et al., 2016). Using the viral strain PRVABC59, isolated from a Puerto Rican patient and genetically close to the strain responsible for the Brazil epidemic, the authors of this study compare the infection levels in six undifferentiated, two terminally differentiated and two retinoic acid-induced partially differentiated neuronal cell lines. With this *in vitro* system, they observe that only the undifferentiated neurons, together with the partially differentiated, are highly susceptive to ZIKV infection, which they confirm by amplification of the viral RNA by real time PCR, immunofluorescence and by evaluation of cytopathic effects by light microscopy. These findings therefore point to a selective sensitivity in ZIKV infectivity due to the degree of neural development, making developing immature progenitor neurons found in the fetus more sensitive to it than the mature neurons from adults. These results are also in agreement with several recent studies performed both *in vivo*, in mouse embryonic brain (Li et al., 2016) and *in vitro*, in human brain development models (human cerebral organoids, human neurospheres or human cortical neural progenitors) (Dang et al., 2016; Garcez et al., 2016; Qian et al., 2016). In these studies, the effect of ZIKV during neurological differentiation is investigated, and demonstrate that ZIKV replicates efficiently in neural progenitor cells (NPCs), leading to cell death and decreasing proliferation and neuronal cell-layer volume, affecting brain development, and therefore promoting microcephaly (Li et al., 2016; Qian et al., 2016). It has been previously suggested that receptors for flaviviruses as DC-SIGN, TIM-1, TIM-4, Tyro3 or AXL could also be responsible for ZIKV entry

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(Hamel et al., 2015; Nowakowski et al., 2016), and future studies should analyze if the presence and quantity of these receptors could be also a determinant for higher susceptibility to ZIKV infection in immature neural cells. Other factors, such as the ease to cross the fetal hematoencephalic barrier towards the adult should be also taken into account.

These results by Hughes et al. provide another step in the search for a mechanism in ZIKV congenital syndrome, and strengthen the link between the current ZIKV epidemic in Latin America and the occurrence of congenital and other neurological defects.

References

Dang, J., Tiwari, S.K., Lichinchi, G., Qin, Y., Patil, V.S., Eroshkin, A.M., Rana, T.M., 2016. Zika virus depletes neural progenitors in human cerebral organoids through activation of the innate immune receptor TLR3. Cell Stem Cell.

Garcez, P.P., Loiola, E.C., Madeiro da Costa, R., Higa, L.M., Trindade, P., Delvecchio, R., Nascimento, J.M., Brindeiro, R., Tanuri, A., Rehen, S.K., 2016. Zika virus impairs growth in human neurospheres and brain organoids. Science 352, 816–818.

Hamel, R., Dejarnac, O., Wichit, S., Ekchariyawat, P., Neyret, A., Luplertlop, N., Perera-Lecoin, M., Surasombatpattana, P., Talignani, L., Thomas, F., et al., 2015. Biology of Zika virus infection in human skin cells. J. Virol. 89, 8880–8896.

Hughes, B.W., et al., 2016. Infectivity of immature neurons to Zika virus: a link to congenital Zika syndrome. EBioMedicine 10, 65–70.

Li, C., Xu, D., Ye, Q., Hong, S., Jiang, Y., Liu, X., Zhang, N., Shi, L., Qin, C.F., Xu, Z., 2016. Zika virus disrupts neural progenitor development and leads to microcephaly in mice. Cell Stem Cell 19, 120–126.

Nowakowski, T.J., Pollen, A.A., Di Lullo, E., Sandoval-Espinosa, C., Bershteyn, M., Kriegstein, A.R., 2016. Expression analysis highlights AXL as a candidate Zika virus entry receptor in neural stem cells. Cell Stem Cell 18, 591–596.

Qian, X., Nguyen, H.N., Song, M.M., Hadiono, C., Ogden, S.C., Hammack, C., Yao, B., Hamersky, G.R., Jacob, F., Zhong, C., et al., 2016. Brain-region-specific organoids using mini-bioreactors for modeling ZIKV exposure. Cell 165, 1238–1254.

Rasmussen, S.A., Jamieson, D.J., Honein, M.A., Petersen, L.R., 2016. Zika virus and birth defects–reviewing the evidence for causality. N. Engl. J. Med. 374, 1981–1987.