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COMMENTARY

# Zika virus-associated brain damage: animal models and open issues

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The suspected involvement of Zika virus (ZIKV) in the 'epidemics' of microcephaly and Guillain–Barré syndrome among patients from Brazil and French Polynesia is of relevant concern.[1] Within this context, the skyrocketing number of cases of ZIKV-associated microcephaly has become a critical public health issue in Brazil since 2015.[2] In fact, the last report of the Brazilian Ministry of Health, released on 25 June 2016, shows 8165 notified cases, 1638 of which received either a diagnostic confirmation of microcephaly or were classified as central nervous system (CNS) alterations suggestive of congenital infection.[3] The number of ZIKV-associated cases of microcephaly in Brazil is still rising; consequently, the threat to other countries, both in South and North America, has become a major concern.

Therefore, characterizing ZIKV neurotropism and neuropathogenicity, along with the host–pathogen interaction dynamics at the CNS level, should be regarded as crucial issues in the study of ZIKV infection's neuropathogenesis. To this end, valuable insight may be derived from the characterization and development of suitable animal models, both natural and experimental, of ZIKV-associated neurological disease,[1,4] in close agreement with the 'One Health' concept and principles. Three recent experimental studies conducted in mice[5–7] have provided clear-cut evidence that ZIKV is able to cross the placental barrier, thereby reaching the fetal CNS, with subsequent microcephaly occurrence. It is worth mentioning that intrauterine growth restriction has also been reported to be associated with microcephaly in ZIKV-challenged mice,[6,7] in close agreement with the clinical findings obtained in human newborns.[8] Notably, the aforementioned experimental mouse data were corroborated through the use of neurospheres and brain organoids. These elegant and useful investigation 'tools/substrates' confirmed that neural progenitor cells (NPCs) are easily targeted and severely damaged by ZIKV,[6] in agreement with what was reported in previous studies.[9–11] This is likely due to the high expression levels of the tyrosine kinase AXL receptor (AXL receptor, encoded by the *AXL* gene and a member of the Tyro3-Axl-Mer receptor tyrosine kinase subfamily) on the NPC membrane surface,[12] which is necessary for viral entry into host cells.[13]

Before the works cited above were published, the cause-and-effect relationships between ZIKV infection and microcephaly development had yet to be uncovered, and other factors, such as nutritional state, coinfection(s) and previous exposure to other viral pathogens, particularly Dengue virus, had to be ruled out.

Notwithstanding the above, there is much left to be discovered about the neuropathogenesis of ZIKV infection. In this respect, provided that white matter hypomyelination and dysmyelination as well as *corpus callosum* hypogenesis and hypoplasia have been recently described in the brains of ZIKV-infected, microcephaly-affected infants from Brazil,[14,15] we believe it would be important to investigate the simultaneous occurrence of white matter damage, if any, in the brain and spinal cord from ZIKV-infected mice. Indeed, neuronal and glial cell proliferation and migration pathways within the developing brain appear to be altered during ZIKV infection.[14] As a consequence, the role of oligodendrocyte precursor cells (OPCs) in the pathogenesis of the aforementioned myelin damage should receive adequate attention, with ZIKV-challenged mice[5–7] likely representing a very useful model. Because OPCs migrate across the entire CNS during development before differentiating into mature myelinating oligodendrocytes,[16] characterizing ZIKV tropism toward OPCs and mature oligodendrocytes appears to be a crucially important issue in the study of ZIKV-associated myelin damage. Furthermore, given that myelination and oligodendrocyte maturation are thyroid hormone-dependent processes,[17] the thyroid glands from ZIKV-infected mice should also be investigated as putative, additional virus targets.

In conclusion, it should be emphasized that, quite surprisingly, the pathogenetic characterization of ZIKV-associated/related myelin damage has been hitherto largely neglected. On the basis of the above, forthcoming *in vivo* and *in vitro* studies, particularly those aimed at assessing ZIKV tropism toward OPCs and mature oligodendrocytes, along with the expression levels of the AXL receptor on these cells, should be considered among the research priorities in ZIKV infection's pathogenesis. Indeed, providing adequate replies to the aforementioned viral neuropathogenesis-related issues would greatly add to the knowledge of the virus- and host-dependent factors and the mechanisms involved in ZIKV-associated microcephaly and myelinopathy. This would also, among other things, shed light on both the

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occurrence and the pathogenesis of other developmental defects, such as club foot, arthrogryposis and muscle hyperreflexia and hypertonia, which, not uncommonly, are observed in microcephaly-affected newborns.

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