IID: Abstract Writing Exam

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HE, Z., AN, S., CHEN, J., ZHANG, S., TAN, C., YU, J., YE, H., WU, Y., YUAN, J., WU, J., ZHU, X. AND LI, M. (2020) Neural progenitor cell pyroptosis contributes to Zika virus-induced brain atrophy and represents a therapeutic target, *Proceedings of the National Academy of Sciences*, 117(38), pp. 23869 LP – 23878. doi: 10.1073/pnas.2007773117.

Abstract

Zika virus (ZIKV) is associated with congenital neurological malformations with unknown mechanisms, which has caused an increasing number of fetuses born with microcephaly and other congenital malformations during the recent epidemic in the Americas. Previous studies indicate that ZIKV infection induces Caspase-3–mediated apoptosis, a cell death pathway that diminishes cortical layers without inducing inflammatory response. However, the activation of nucleotide and oligomerization domain, leucine-rich repeat-containing protein family, pyrin-containing domain 3 (NLRP3) inflammasome, suggest a role pyroptosis, a highly inflammation-associated programmed cell death in ZIKV infection. Thus, whether and how pyroptosis is involved in ZIKV-induced cell death of brain neural cells needs to be clarified. Here we show cleaved caspase-1 and PI+ cells and significant increase of NLRP3 expression using immunohistochemistry and RT-PCR, respectively in in mice and 3D culture of human neural cells, which indicates ZIKV can induce neural progenitor cell pyroptosis both *in vivo* and *in vitro*. Besides, immunoblotting reveals significant caspase-1 and GSDMD cleavages, which suggest caspase-1 mediates pyroptosis in ZIKV infection. Furthermore, genetic knockout of caspase-1 and pharmaceutical inhibition of caspase-1 with caspase-1 inhibitor VX-765 are both found to alleviate neuropathology and brain atrophy in mice. These results show a previously unknown mechanism of caspase-1–mediated pyroptosis that causes ZIKV-induced neuropathological effect during development, which also supports selective inhibition of caspase-1 using VX-765 to be a potential treatment to alleviate ZIKV-induced neurodevelopmental brain damage.

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