

## **25-HYDROXYCHOLESTEROL PROTECTS HOST AGAINST ZIKV INFECTION AND ITS ASSOCIATED MICROCEPHALY**

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Zika virus (ZIKV) became a global public health threat due to its global transmission and unexpected link to severe congenital diseases. Protective host immune responses are poorly understood and ZIKV therapeutics are still in development. We found that Cholesterol-25-hydroxylase (CH25H) is strongly induced in response to ZIKV infection through the Type I interferon dependent pathway and play a critical role in host defense against ZIKV infection through its production of 25-hydroxycholesterol (25HC). Furthermore, we have demonstrated that the synthetic 25HC significantly inhibits ZIKV infection in vitro and in mouse and rhesus macaques. Importantly, 25HC suppresses ZIKV infection and reduces tissue damage in both human cortical organoids and the embryonic brains of a ZIKV-induced mouse microcephaly model. Our findings therefore highlight the protective role of CH25H during ZIKV infection, and suggest the potential use of the naturally produced broad antiviral agent 25HC to inhibit ZIKV infection and prevent ZIKV-associated diseases such as microcephaly.