Supplement could protect against fetal Zika infection

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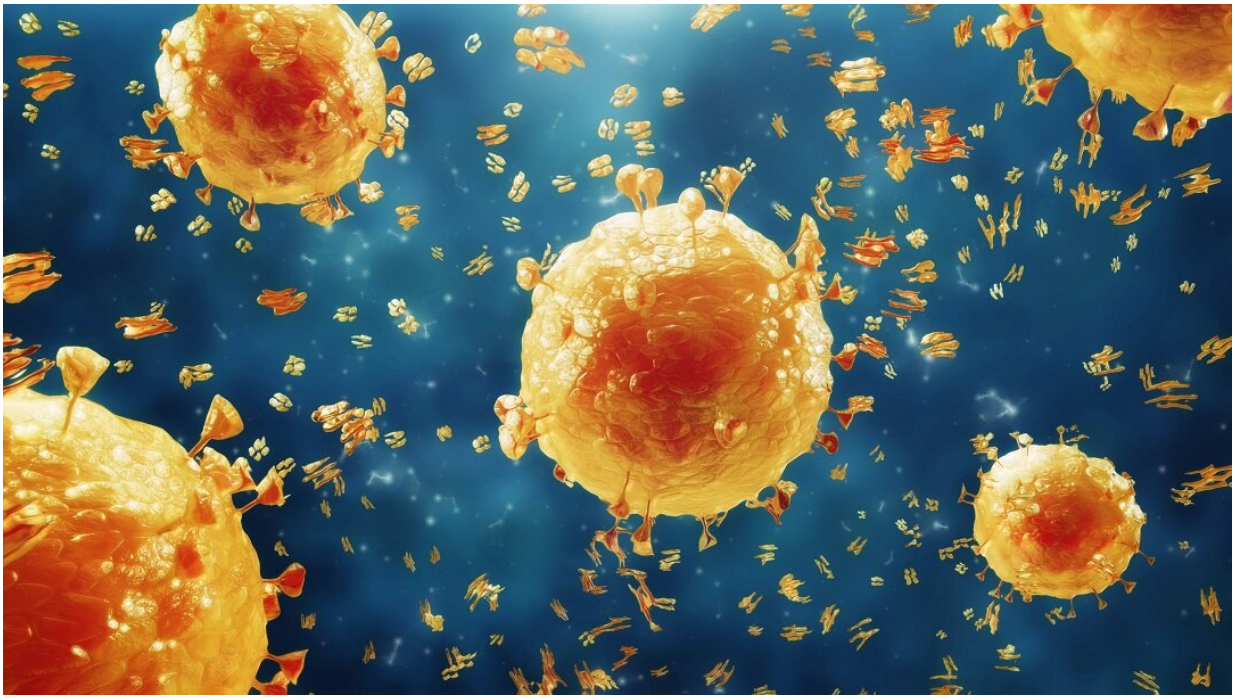

Credit: Duke-NUS Medical School

The Zika virus shunts carbon atoms away from the important glucose metabolism pathway in infected fetuses, leading to a cascade of events that significantly impact fetal development. But giving pregnant mothers a readily available supplement could protect their babies, say the Singapore scientists who made this discovery.

The researchers from Duke-NUS Medical School and their collaborators published their findings today in the journal *Cell Reports*.

In 2016, the World Health Organization declared a rise in Zika-virus-related neurological disorders and malformations in newborn babies as a public health emergency of international concern. Generally, infection occurs via Zika virus-carrying mosquito bite. The virus can then be transmitted to other people during sex or from blood transfusion. Infected women can transmit the virus to their fetus during pregnancy.

When a fetus becomes infected, the baby can be born with an abnormally small head or other birth defects, and may even die. Researchers set out to understand how Zika virus infection causes congenital Zika syndrome in order to find ways to prevent it.

"We wanted to identify the minimal set of host responses to Zika virus infection that are necessary for a disease outcome," said Professor Ooi Eng Eong, from Duke-NUS Medical School in Singapore, the lead investigator and senior author of the study. "Doing this could help develop effective treatments against congenital Zika syndrome or even a safe vaccine for use in pregnant women."

The team did this by investigating how cells and their genes responded when they were infected by a spectrum of weakened to fully virulent strains. They had discovered a critical gene change that turns the Zika virus from its weakened to a mildly pathologic form.

They found that the viral load of this mildly pathogenic strain of the virus, named M-F37L, was less than that of the fully virulent one but more than that of the weakened one. It also had the same lethal consequences for the fetuses as the wild-type virus. This suggested that M-F37L could be used to represent the point where viral infection becomes pathologic for the host.

Subsequent gene and cell studies showed that infection with M-F37L disrupted the glucose metabolism pathway that is vital for nerve development. Disrupting the pathway impacted mitochondrial function and ultimately led to cell inflammation and death.

Using an animal model conducted according to the National Advisory Committee for Laboratory Animal Research (NACLAR) guidelines, the team discovered that supplementing cells and also pregnant mice with a downstream compound in the glucose metabolism pathway, called pyruvic acid, could restore mitochondrial function and reduce the impact of Zika virus infection on fetal development.

Further investigations are needed to understand what doses of pyruvic acid pregnant women may have to take to protect fetuses from these adverse developmental impacts. The team is also interested in further understanding how the Zika virus manipulates glucose metabolism and will investigate whether dengue viruses, which are genetically related to the Zika virus, also manipulate glucose metabolism in the same way.

Professor Patrick Casey, senior vice-dean for research at Duke-NUS, said, "Even as COVID-19 dominates public interest, the Zika virus continues to pose a serious threat to public health around the world—such as in India, which is currently experiencing an outbreak. This research by Prof Ooi and his collaborators highlights the ceaseless vigilance of the scientific community against all diseases of public health concern, and the constant search for the means to control them."

More information: Clement Yau et al, Dysregulated metabolism underpins Zika-virus-infection-associated impairment in fetal development, *Cell Reports* (2021). DOI: 10.1016/j.celrep.2021.110118

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