Mother's dengue immunity worsens baby's response to Zika

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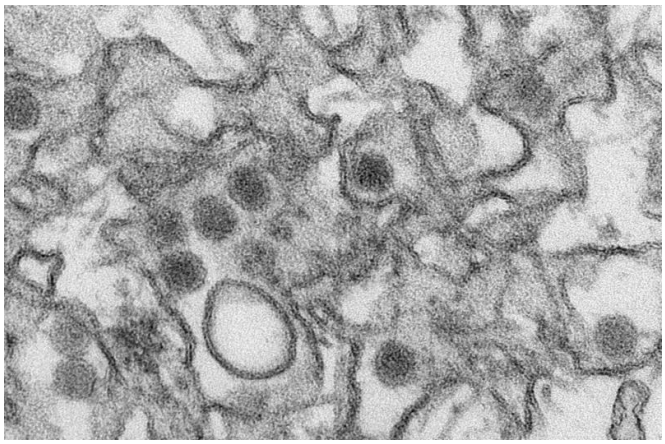

Transmission electron micrograph (TEM) of Zika virus. Credit: Cynthia Goldsmith/Centers for Disease Control and Prevention

Researchers at Duke-NUS Medical School and their colleagues have identified a surprising interaction between dengue and Zika viruses that sheds lights on the significant fetal brain abnormalities linked to Zika virus.

The researchers found that fetal mouse brain damage was much worse if the mothers infected with Zika also had dengue antibodies. They further determined that an immune complex that forms when dengue antibodies attach to the Zika virus is recognized by a receptor on placental cells, allowing the virus to travel across the placenta into fetal cells. Their findings are reported in the journal *Science Advances*.

Asst Prof St. John and a team of researchers in Singapore wanted to investigate why some, but not all, Zika virus infections during pregnancy led to fetal brain abnormalities. They also wanted to know if the severity of fetal infection had anything to do with previous infection of the mother with dengue virus, which is closely related to Zika and often circulates in the same regions of the world.

"Our research indicates that previous immunity of the mother to dengue could be a risk factor for severe outcomes in infants born to mothers infected with Zika virus during pregnancy," said Assistant Professor Ashley St. John, from Duke-NUS' Emerging Infectious Diseases (EID) Programme and the corresponding author of the study. "This is highly significant, since current Zika virus epidemic regions overlap to large extent with those of dengue viruses, and this work informs our understanding of mechanisms that could influence the severity of infection with Zika virus."

The study, which employed an animal model conducted according to the National Advisory Committee for Laboratory Animal Research (NACLAR) guidelines, analysed the physical differences between the fetuses of mothers who had never been exposed to dengue, or had dengue and had developed antibodies against the virus.

The team found that Zika virus infection in mothers with antibodies against dengue resulted in fetuses with smaller body mass and head circumferences, and more significant damage to the brain tissue. Further, when a receptor called neonatal Fc receptor (FcRN), was blocked, Zika virus transmission from mother to fetus was reduced, resulting in a larger head circumference and less brain damage.

The team also showed that antibodies to dengue can promote transmission of Zika virus across human placental cells, but further research is needed to determine if previous dengue virus infection has the same effect on human babies born to women infected with Zika during pregnancy.

The novel mechanism that leads to Zika virus transfer from mother to fetus could also be relevant in other viral infections that can also be transmitted from mother to fetus, such as HIV and

cytomegalovirus, says St. John.

Commenting on the findings, Prof Patrick Casey, Senior Vice Dean of Research, Duke-NUS Medical School, said, "Innovative research conducted by our Emerging Infectious Diseases Programme has yet again resulted in new knowledge that helps us better understand viruses like Zika and dengue. This study sheds light on a question that has, until now, eluded doctors and researchers—the mechanism behind why some babies of mothers exposed to Zika are born with brain abnormalities—and is a critical step in finding new options for prevention and treatment."

The team next aims to employ their findings to develop better treatment options for Zika virus infection during pregnancy.

More information: Abhay P. S. Rathore et al, Maternal immunity and antibodies to dengue virus promote infection and Zika virus–induced microcephaly in fetuses, *Science Advances* (2019). DOI: 10.1126/sciadv.aav3208

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