NBRC researchers decipher how Zika virus causes microcephaly

National Brain Research Centre-led team of researchers has successfully identified the molecular and cellular mechanisms by which Zika virus causes microcephaly. Babies born with microcephaly have significantly smaller head size compared with normal babies. The researchers found the envelop protein (E protein) of the virus, which is responsible for the entry of the virus into brain stem cells, was responsible for arresting the proliferation of human foetal neural stem cells and also killing the cells that were becoming neuron-like. The combined effect reduces the pool of foetal brain cells leading to smaller size of the brain.

“Though more studies are required, neutralising the E protein of the virus can help prevent or reduce the harmful effects of the virus in a developing foetus. The E protein can be seen as a likely therapeutic target,” says Dr. Pankaj Seth from the Department of Cellular and Molecular Neuroscience at NBRC and corresponding author of a paper published in the journal *Cell Death & Differentiation*.

The E protein in Zika virus is mutated and very different from the envelop protein of other flaviviruses such as dengue, West Nilevirus, yellow fever and Japanese encephalitis.

“When four proteins that have already been identified in other flaviviruses were over-expressed [produced in excess], the E protein was found to be more potent in arresting the proliferation of brain stem cells. The other three proteins were acting in a less significant manner. So we chose to further study the E protein. We also sequenced the RNA of stem cells after exposure to E protein to understand how the stem cell RNA gets affected,” says Reshma Bhagat from NBRC and first author of the paper.

On sequencing the RNA, they found 25 microRNA of stem cells were either expressed in excess or very little in the presence of the E protein. Two of the microRNAs regulate the expression of human genes and play an important role in brain development and maintaining the ability of stem cells to renew themselves (stemness).

When stem cells start dividing, one cell goes into self renewal and becomes a stem cell while the other follows the lineage to become some kind of a brain cell. “What we saw is when the E protein is over-expressed inside stem cells, it promoted premature but faulty formation of neurons. They start becoming a neuron-like cell but the entire process of becoming a neuron cell is not completed successfully and so is faulty and they tend to die naturally,” says Dr. Seth.

While the E protein was unable to kill the stem cells as they are lot more resilient, it was able to kill the neurons. “Neurons are more susceptible to neurotoxin and don’t divide. So there are fewer brain cells leading to smaller size of the brain,” he adds.

To validate the findings, the researchers in collaboration with Prof. Jonaki Sen at the Indian Institute of Technology (IIT) Kanpurintroduced the E protein in pregnant mice at 13.5 days gestation and harvested the brain two days later. “We saw the stem cells had reduced in number and they weren’t proliferating,” says Bhagat.

Other researchers had introduced the virus in brain stem cells and found the proliferation of stem cells getting inhibited. “But no one was aware which component of the virus was causing the problem. Our study has solved the puzzle,” says Dr. Seth.

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