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Research sheds new light on virus associated with developmental delays and deafness; Offers hope for treatment

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A new study published online in *PLOS ONE* reveals that primitive human stem cells are resistant to human cytomegalovirus (HCMV), one of the leading prenatal causes of congenital intellectual disability, deafness and deformities worldwide. Researchers from the University of Pittsburgh School of Medicine found that as stem cells and other primitive cells mature into neurons, they become more susceptible to HCMV, which could allow them to find effective treatments for the virus and to prevent its potentially devastating consequences.

"Previous studies have focused on other species and other cell types, but those studies did not evaluate what the cytomegalovirus does to human brain cells," said Vishwajit Nimgaonkar, M.D., Ph.D., professor of psychiatry at the University of Pittsburgh School of Medicine, and senior author of the report. "This study is the first of its kind, and the first to discover that primitive stem cells are actually resistant to HCMV."

Access to cultured human neurons, necessary to understand the pathogenic effects of HCMV, has been limited by difficulties in growing the brain cells in the laboratory. Yet through human-induced pluripotent stem (iPS) cells, researchers were able to overcome this hurdle.

The study authors derived live iPS cells by reprogramming cells called fibroblasts obtained from human skin biopsies. The iPS cells were then

induced to mature through several stages into neurons, the primary cells in the brain. The researchers were able to evaluate the patterns of damage caused by HCMV on all these cells.

The research findings suggest:

- Human iPS cells do not permit a full viral replication cycle, suggesting for the first time that these cells can resist CMV infection
- CMV infection distorts iPS cell differentiation into neurons, and that may be a mechanism by which infected babies develop impairments of brain maturation and intellectual ability
- iPS-derived mature neurons are more susceptible to CMV infection and once infected show effects including defective function that have been shown in other animal studies and in other human tissues, and the neurons die a few days after infection lab studies, possibly reflecting the impact of CMV on the human brain

"The findings were quite surprising, but this is only the first in a series of studies on HCMV," added Nimgaonkar. "There is a lot of interest in what we can do to treat the infection, and current work is already underway to screen for new drugs that could be used to fight these viruses."

Between 50 and 80 percent of people in the U.S. have been infected by HCMV by the time they reach 40. Infections are rarely serious, but the virus does not leave the body. CMV is also the most common congenital infection in the U.S., and occurs when a mother contracts CMV during pregnancy and passes the virus to her unborn child. According to the U.S. Centers for Disease Control and Prevention, one of every 150 children is born with CMV infection and one in five of them develops

permanent problems, such as intellectual disability, vision and hearing loss, and seizures.

Pitt researchers are collaborating with the Drug Discovery Institute to further understand the cellular system and determine which agents are most effective against HCMV and similar viruses, and which treatments would be safe for human use.

Provided by University of Pittsburgh Schools of the Health Sciences