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Research points to potential window for treating CMV and preventing mother-to-child transmission

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New insights into how human cytomegalovirus (CMV), the leading cause of birth defects associated with infection spreads from pregnant mother to fetus and from organ to organ in newborns provides translational researchers an exciting new avenue for investigation that may lead to the development of therapeutic interventions. Using next generation sequencing and population genetic modeling, scientists at the University of Massachusetts Medical School (UMMS) and the Ecole Polytechnique Fédérale de Lausanne (EPFL) have found that CMV evolves rapidly and dramatically in humans. These findings, published in *PLoS Genetics*, provide new genetic targets that could impede the evolution of CMV and prevent its spread.

"These findings have important implications for how we think about and develop new therapeutic treatments for CMV," said Timothy F. Kowalik, PhD, associate professor of microbiology and physiological systems and senior author of the study. "Although CMV is able to infect a wide variety of organs throughout the body, there are a substantial number of genetic changes that occur before the virus can spread and replicate efficiently in different anatomic niches. If these genetic changes can be prevented, it may be possible to isolate and block the spread of CMV."

CMV is a ubiquitous virus that infects most of the human population and can move throughout the body from organ to organ. Infection is usually

asymptomatic in healthy hosts, but may cause severe symptoms for patients with a compromised immune system, such as organ transplant recipients, HIV-infected persons, newborn infants or the fetus during gestation.

Congenital CMV infection, which is passed from a pregnant mother to fetus, is a significant cause of birth defects, and remains a high priority for vaccine development according to the nonprofit, Institute of Medicine. An estimated 30,000 infants per year in the U.S. are diagnosed with congenital CMV infection, and nearly 20 percent exhibit permanent neurologic effects such as hearing loss or developmental delay.

To better understand how CMV evolves in fetuses and newborns during symptomatic congenital infection, researchers at UMMS and the University of Minnesota Medical School collected samples from the plasma and urine of five congenitally infected infants during the first year after birth. Using next generation DNA sequencing, Kowalik and colleagues studied the diversity and changes in viral DNA sequences over time and between organs. Though the DNA sequences from viruses taken from the same type of sample (e.g. plasma) were similar to each other, the study's authors found dramatic differences between the sequences collected from viruses in the plasma and urine of the same infant. Surprisingly, the plasma and urine sequences from the same infant were as different as sequences from two unrelated infants.

These results suggest that CMV is able to evolve very quickly as the differences between the plasma and urine sequences likely occurred in the short period between the initial, in utero infection, and the first year after birth. However, the mechanism driving this phenomenon remained unclear.

To answer this question, researchers used mathematical modeling and

statistical inference to uncover evidence that population bottlenecks and expansions may play a significant role in the virus' evolution after infection. Characterized by a substantial reduction in viral copies followed by a quick rebound, population bottlenecks and expansions can lead to dramatic changes in DNA sequences that result in two related populations quickly becoming dissimilar. In the case of CMV infection, this phenomenon appeared to coincide with the virus moving from the mother to the fetus and later migrating from the plasma to the kidneys.

The model also suggests that the timing of initial fetal infection in the patients was at 13 to 18 weeks gestational age, while viral spread from blood plasma to the kidneys occurred about 11 weeks later. "This timing," said Kowalik, "may provide an important window for treating CMV when it is most vulnerable and before it can evolve and spread."

Additional study showed that natural selection, the process through which certain advantageous biological traits become more common, results in as much as 20 percent of the viral genes changing as it moved from one biological niche to another. "Not surprisingly, the genes impacted by this selection process affect several viral functions involved in dissemination, including viral replication in distinct cell types and evasion of the host immune response, and are required to allow the virus to move to and replicate efficiently in different organs," said lead author of the study, Nicholas Renzette, PhD, a postdoctoral fellow at UMMS.

This new understanding of how CMV adapts and evolves after infection provides researchers with potential targets for treating the disease, said Kowalik. "This work shows that CMV infection spreads during a relatively small window during gestation, suggesting an opportunity for preventative treatments," he said. "Furthermore, the delay between initial fetal infection and dissemination to the kidneys, may present a window for stopping spread of the virus throughout the body, thereby preventing symptoms of infection, such as hearing loss."

The next step for Renzette, Kowalik and colleagues is to determine which genetic changes associated with immune responses to infection may be amendable to potential treatments.

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