Monkey model discovery could spur CMV vaccine development

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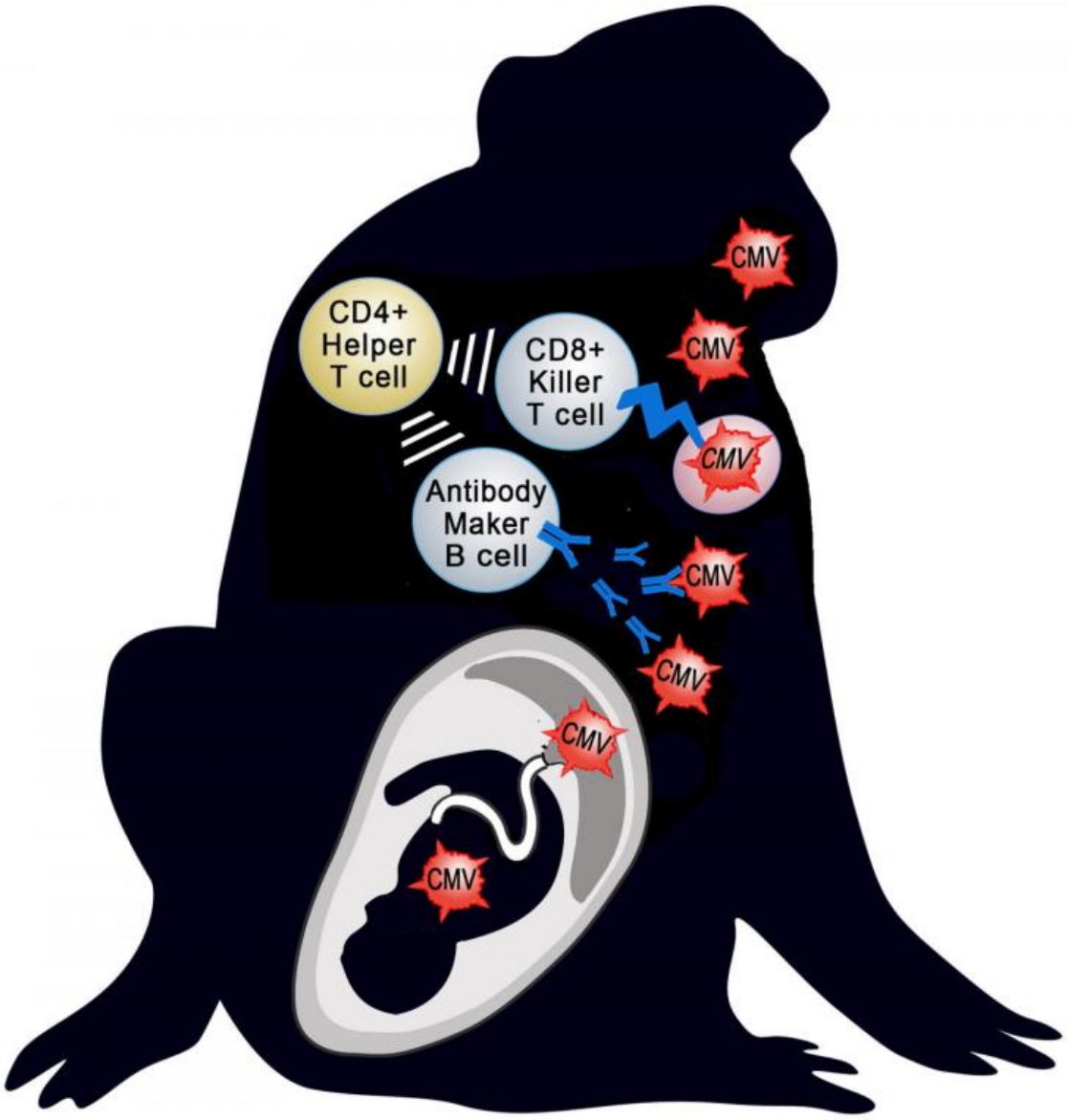

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disarm the pathogens en route. Credit: Mark Dubowski

Cytomegalovirus (CMV) is the leading infectious cause of birth defects worldwide, but scientists have been frustrated in their efforts to develop a vaccine to protect against infections.

Among the most confounding problems is the lack of animal models that aptly mimic CMV passing from mother to unborn child, as it does in humans. Aside from guinea pigs, which have limited similarities to humans, no other mammals were known to pass the virus to their fetuses.

Or so it seemed.

Now researchers at Duke Medicine have discovered that rhesus monkeys can, in fact, transmit the virus across the placenta to their unborn offspring. This finding, reported online during the week of October 19 in the *Proceedings of the National Academy of Sciences*, establishes the first primate model that researchers can use to study mother-to-fetus CMV infections and spur development of potential vaccine approaches.

"A huge impediment to CMV vaccine development has been our lack of ability to determine what immune responses would be needed to protect against mother-to-fetus transmission," said senior author Sallie R. Permar, M.D., Ph.D., of the Duke Human Vaccine Institute. "This requires good animal models, where we can manipulate each arm of the immune system to evaluate its role in congenital infection."

CMV is related to the herpes viruses that cause chicken pox and mononucleosis, and in most people, it results in mild to no symptoms of disease when they acquire an infection. However, in about a third of instances when women who have never been exposed to CMV contract

the virus during pregnancy, they can pass an infection to the fetus. About a quarter of those infants will go on to have neurologic impairment.

The Centers for Disease Control and Prevention reports that about 5,000 children a year in the U.S. are born with permanent problems resulting from CMV infections, including deafness, blindness, seizures and cognitive delays.

"This is a situation of great concern and we need to work to prevent it," Permar said. "After the rubella vaccine was developed in the 1960s, schools for the deaf and blind had to close their doors because there were far fewer children who had suffered congenital rubella infections and needed the services. That's the kind of impact a CMV vaccine could have."

Permar said simple approaches to vaccine development, such as creating a weakened virus to trigger immunity, have failed, because the virus has evolved alongside humans to elude the immune system. So having a non-human primate model - something of a higher order than guinea pigs - became imperative.

Permar said finding the mother-to-fetus transmission in the rhesus macaques became a hunt. She enlisted the help of co-senior author Amitinder Kaur of Tulane National Primate Research Center, an expert in CMV-specific immunity in rhesus macaques.

Most macaques are infected with the rhesus version of CMV before adulthood, yet their young are born without the hearing loss or neurological problems that human babies can acquire in utero. In an earlier study, coauthor Peter Barry of the University California at Davis found that infection of a macaque fetus directly through the abdomen resulted in a similar disease to that in humans. Permar and Kaur wanted know if the infection could pass through the placenta.

Using macaques at the New England Primate Research Center, Harvard Medical School, that were specially bred to be free of CMV and all herpes viruses, they depleted the CD4 "helper" T cells that play an important role in antibody responses. When infected with CMV a week later, all the animals passed the virus through the placenta, resulting in miscarriage in three of the four animals.

"This told us not only that the virus could be transmitted through the placenta, but that the mother's immune system was playing an important role in the severity of the infection," Permar said.

In a second experiment, Permar and Kaur infected CMV-negative animals with the virus, and left their immune systems intact. Among this group, CMV was transmitted to two of three offspring in utero, but the animals were born with no major neurological deficits - mimicking what often occurs in humans.

In a third control group of animals, the researchers studied females that had naturally been infected with CMV earlier in their lives, and depleted their CD4 helper T cells during pregnancy. The mothers had little to no circulating virus and the offspring appeared to be unaffected by the CD4 helper T cell depletion.

"In addition to establishing a primate model for congenital infection, we gained new information about the importance of the maternal immune system in protecting the fetus," said lead author Kristy Bialas, a post-doctoral fellow at Duke. "Whereas CMV transmission among immune-competent mothers did not result in fetal disease, transmission in mothers with compromised T cell immunity led to severe fetal outcome."

Permar said the next stage of research will be to determine whether neutralizing antibody responses would be enough to protect against

transmission of severe disease, or whether a T-cell vaccine would be the better approach.

More information: Maternal CD4+ T cells protect against severe congenital cytomegalovirus disease in a novel nonhuman primate model of placental cytomegalovirus transmission, www.pnas.org/cgi/doi/10.1073/pnas.1511526112

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