Research opens door to vaccines that can circumvent maternal antibodies

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New research that reveals how maternal antibodies block an immune response to the measles virus is a first step toward improving current childhood vaccination practices, scientists say.

Maternal antibodies are passed to fetuses during pregnancy and to newborns in their mothers' milk. The antibodies protect infants against disease in the first months of life, but that protection comes at a cost: Their presence also interferes with the generation of a natural immune response to vaccination. As a result, most babies receive measles immunizations at the age of 12 to 15 months, when maternal antibodies are gone.

Years of studies have advanced the theory that maternal antibodies shield the measles virus so that cells that generate an immune response can't see the pathogen. If that were the case, little could be done to intervene.

But Ohio State University researchers have demonstrated an entirely different mechanism in an animal model, showing that maternal antibodies bind to a specific receptor that sends a message to stop activation of an immune response to vaccination. The scientists also determined that signals to the immune response can be manipulated, and they are already devising ways that vaccines could be designed to circumvent this natural process.

"In effect, we have found how maternal antibodies affect the off-switch

in the immune response, and we have found a potential on-switch," said Stefan Niewiesk, associate professor of veterinary biosciences at Ohio State University and senior author of the study.

The research is published in the online First Edition of the journal *Blood*.

Under current pediatric practices, children receive measles vaccinations at age 12 to 15 months, and again when they are 5 years old. Maternal antibodies can be active in babies for up to nine months; this schedule is designed to offer protection after the decline of maternal antibodies.

"The maternal antibodies are high at birth, and go down over time. By age 1 year, the maternal antibodies are gone. So this vaccine schedule works quite well if protection is not so urgent. But there is a window of opportunity for measles to come in and infect. So we would like to be able to immunize earlier," said Niewiesk, also an investigator in Ohio State's Center for Microbial Interface Biology.

Niewiesk has been a leader in developing the cotton rat as an animal model for infectious diseases. The animal is susceptible to common human pathogens that affect the respiratory system, and Niewiesk's lab has developed antibodies and other substances that help to evaluate the immune response, which is similar to that found in humans.

As a result, researchers around the world have consulted with Niewiesk for years, using the animals to test vaccine candidates. Often, the experimental vaccines do not work in the presence of maternal antibodies. And even for the one vaccine that did work, the researchers couldn't explain why at the time.

So Niewiesk changed direction, setting aside vaccine testing and instead studying how the maternal antibodies influence the immune response to

an antigen – in this case, the measles virus. With this new information, he and colleagues now have better information to guide the design of a measles vaccine that will be effective even while maternal antibodies are present.

In a normal immune response, white blood cells known as B cells grow and release antibodies that are prepared to fight a specific invader, known as an antigen. The B cells are called to action by B cell receptors on their surface; when the antigen binds to these B cell receptors, the cells get the message to proliferate and then secrete antibodies that are made strictly for the task of fending off the attacking virus.

But the Ohio State researchers determined that when maternal antibodies are active, and then an antigen comes along, their presence triggers a different receptor on the B cell surface – a receptor known as Fc-gamma RIIB. And because this particular receptor's job is to regulate the immune response, preventing it from going out of control, the receptor tells the B cell to stop – don't grow, and don't secrete antigen-specific antibodies.

"The problem is that maternal antibodies come in, and will go away, but this Fc receptor doesn't know it. The receptor reacts – 'Hey, there is antibody already, let's not make too much of an immune response.' This binding leads to a negative signal, and it blocks the receptor's positive signal to the B cell," Niewiesk said.

Further investigation of the multiple signals received by B cells suggests that there are ways to work around this effect that the maternal antibodies have on the immune response, said Dhohyung Kim, first author of the paper and a doctoral candidate in Ohio State's graduate program in Molecular, Cellular and Developmental Biology.

Maternal antibodies are immunoglobulin G (IgG) molecules, a

designation based on their structure, and IgG antibodies are among the most potent players in the immune response. In this current work, Kim showed that another type of antibody, an immunoglobulin M molecule, can be used with a measles vaccine and that these IgM antibodies can activate B cells, even when maternal antibodies are present.

The IgM antibodies bind to yet another type of receptor on the B cell surface, Niewiesk explained. "So we are looking at the various ways B cells are being activated, and we already see that we can improve the positive signal to B cells by stimulating them with IgM antibodies," he said.

As part of the study, the researchers disproved the previous theory about how maternal antibodies work – a process called epitope masking. This theory suggested that maternal antibodies would bind to specific areas on the measles virus needed for immune response recognition – called epitopes – and effectively shield the virus so that B cells could neither see the virus nor activate an immune response.

Niewiesk said the scientists knew that the measles virus surface has numerous epitopes, making it highly unlikely that maternal antibodies could block so many different areas of recognition on a single virus. In addition, they showed that suppression of the immune response did not occur if maternal antibody structures were manipulated to prevent them from binding to the Fc-gamma RIIB receptor. That meant that this Fc receptor was key to the mechanism that allowed maternal antibodies to suppress the immune response.

Provided by The Ohio State University

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