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New insight on maternal infections and neurodevelopmental disorders

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The immune responses of a female mouse before pregnancy can predict how likely her offspring are to have behavioral deficits if the immune system is activated during pregnancy, according to researchers from the Center for Neuroscience at the University of California, Davis. The findings, published April 23 in the journal *Brain, Behavior, and Immunity*, could help resolve what role serious infections during pregnancy play in the later development of conditions such as autism and schizophrenia in offspring.

Both genetics and a variety of environmental risk factors are thought to play a role in mental illness, said Professor Kim McAllister, director of the Center for Neuroscience and senior author on the paper. Most pregnancies are resilient, she said. Although the risk from maternal immune activation is low, it could provide a way in to the underlying problems that lead to schizophrenia or autism.

"We don't have a good handle on what causes these diseases," she said. "But, maternal infection is a risk factor that we know contributes. So, our research focuses on how to predict which pregnancies are at risk and discover new ways to intervene and prevent disease in offspring."

The first evidence for a role for maternal infection in mental and developmental disorders came from the influenza epidemic of 1918, McAllister said. Epidemiological studies 15 to 20 years later of children who were in gestation at the time showed an increase in these disorders. Other evidence comes from animal studies.

Mouse model of immune activation

Apart from influenza, a wide variety of viruses and bacteria have been implicated in maternal immune activation. So the effect is more likely due to the mother's reaction to infections than with the infectious organism itself.

To reproduce this in mice, McAllister's team doses pregnant mice with a molecule called polyinosinic:polycytidylic acid, or poly (I:C), which is double-stranded RNA, the genetic material for many viruses including influenza and coronaviruses. The immune system recognizes poly (I:C) as if it were a virus and triggers an immediate inflammatory response, especially releasing a molecule called interleukin-6, or IL-6.

The mice continue with pregnancy and when the offspring are about 2 months old, the researchers test them for behavioral abnormalities, such as repetitive behaviors or freezing in place.

One of the advantages of working with laboratory mice is that they are bred so that they are genetically very similar. That makes it easier to see the effect of particular genes or environmental risk factors.

But when graduate student Myka Estes tried to treat laboratory mice with poly (I:C), she found to her surprise that their responses varied widely, even though the mice were all of the same age and genetic background, housed in the same cages in the same conditions.

Professor Judy Van de Water, an immunologist at the UC Davis School of Medicine and part of Estes' thesis committee, suggested looking at baseline immune reactivity in the mice before they became pregnant.

When they did that, the team found that the IL-6 response of a particular mouse to poly (I:C) before it became pregnant could predict the

likelihood of behavioral problems in offspring if the mouse were treated with poly (I:C) later during pregnancy.

"People assume that their mice are all the same, but there is clearly a wide range of baseline immunoreactivity," McAllister said. That baseline immunoreactivity turns out to predict resilience or susceptibility to immune activation during pregnancy.

"We can dose them with poly (I:C) and look at the IL-6 response and predict which ones will have affected offspring if we treat them during pregnancy," she said.

Basic mechanisms and biomarkers

That has a couple of important implications. Firstly, with a reliable model for resilience and susceptibility, researchers can start to work out what genes and proteins involved in brain development are affected by immune activation and how this could lead to neurodevelopmental disorders.

"The next steps are to figure out what it is that is different about those mice," McAllister said. "Now that we can predict which mice are at risk, we want to determine how specific patterns of immune signaling in the mom cause distinct outcomes in offspring. We are hoping to figure out how maternal infection can lead to no problem in many pregnancies and to a range of distinct diseases in offspring from other pregnancies."

Secondly, it could lead to biomarkers for identifying pregnancies at higher risk from infections and taking steps to protect mothers by vaccination or treatment. That will likely involve further work in mice followed up with experiments in nonhuman primates before moving into human studies.

More information: Myka L. Estes et al, Baseline immunoreactivity before pregnancy and poly(I:C) dose combine to dictate susceptibility and resilience of offspring to maternal immune activation, *Brain, Behavior, and Immunity* (2020). DOI: 10.1016/j.bbi.2020.04.061

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