NEWS

Blocking key immune signal prevents autism signs in mice

BY **ANN GRISWOLD**

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Researchers have identified a key immune molecule in pregnant mice that produces autism-like behaviors in their pups. The findings, published 28 January in *Science*, support the theory that infections during pregnancy raise the risk of autism[1]. The study also hints at a way to mitigate the risk.

“Somewhere down the road, if this applies to human physiology, it may be possible to prevent autism by treating women who have elevated levels of [the immune signal],” says lead researcher **Dan Littman**, professor of immunology at New York University.

An infection during pregnancy **raises the risk of having a child with autism by 37 percent**; women with an overactive immune system **also have a heightened risk**. How an immune reaction might spur autism is unclear, but some studies have found elevated levels of interleukin-17 (IL-17) — a signaling molecule that helps to fend off foreign invaders — in children with autism[2].

Mouse studies also support this theory. Pups born to pregnant mice exposed to a mock virus **have autism-like characteristics**, such as social deficits and **repetitive behaviors**.

In the new study, Littman and his colleagues show that blocking IL-17A — a subtype of IL-17 — in infected pregnant mice prevents these symptoms in their pups.

IL-17 plays a key role in autoimmune diseases such as multiple sclerosis, lupus and rheumatoid arthritis[3]. Women with these conditions **have an increased risk of having a child with autism**.

“This work provides further evidence for a role of maternal infection and inflammation in autism and suggests potential therapeutic targets in this disorder,” says **Alan Brown**, professor of psychiatry and epidemiology at Columbia University, who was not involved in the research.

Signal malfunction:

Littman and his team created mice lacking the cell type that produces IL-17A. They injected these mice, as well as controls, mid-pregnancy with a molecule that mimics a viral infection.

Consistent with previous work, pups born to the control mothers performed poorly on tests of social behaviors (time spent interacting with other mice), communication (number of high-pitched squeaks) and perseveration (time spent burying a marble). The mice also showed signs of abnormal brain development: The layers of the brain's outer shell, called the cerebral cortex, appear disorganized.

By contrast, pups born to mothers that lack IL-17A performed normally on all of the tests. The researchers saw similar results when they treated controls with antibodies that block IL-17A.

They injected IL-17A directly into fetal mouse brains and found that doing so could produce abnormal cortical layering and autism-like behaviors, even without a maternal infection. This finding suggests that maternal IL-17A leads to autism by acting in the fetal brain, rather than through the mother.

"This is a very elegant study for understanding how important the maternal immune system is for fetal brain development," says **Betty Diamond**, head of the Center for Autoimmune and Musculoskeletal Disorders at the Feinstein Institute for Medical Research in Manhasset, New York, who was not involved in the study.

On target:

Littman says his team was surprised that an immune molecule from the mother binds to a protein in the fetal brain, and that it might shape fetal brain development as a result. It's possible that the receptor has roles beyond binding IL-17, he says.

"The more we learn about the connection between the immune and central nervous systems, the more we'll understand disorders such as autism that target both of them," says **Jonathan Kipnis**, professor of neuroscience at the University of Virginia in Charlottesville, who was not involved in the study.

Whether this maternal-fetal immune connection exists in people remains to be seen, however. Researchers still aren't sure which brain cells express the IL-17A receptor in mice, so they don't know whether the same cells express the receptor in people. It's also unclear whether IL-17A levels are elevated in pregnant women who give birth to children with autism.

"It's far too early to determine whether this pathway will apply to humans, but it certainly opens up a potential avenue of research that should be looked at carefully," says **Sarah Gaffen**, professor of

rheumatology and clinical immunology at the University of Pittsburgh, who was not involved in the work. “This is a beautiful and intriguing study.”

REFERENCES:

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