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Certain viral infections during pregnancy could cause behavioral changes in offspring

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A study published in the journal *Science* found that activation in pregnant mice of a particular immune response, similar to what may occur with certain viral infections during pregnancy, alters the brain structure of the mouse offspring and causes behavioral changes, reminiscent of those observed in humans with autism spectrum disorder (ASD).

Several past human studies have suggested a correlative link between maternal viral infection during pregnancy and risk of autism spectrum disorder. Mouse models have been created and used to study how maternal immune activation influences autism-like behavior, but the mechanism underlying this was not known until now.

The study, "The maternal interleukin-17a pathway promotes autism-like phenotypes in offspring" published on Jan. 28 in *Science*, and led by researchers from the University of Massachusetts Medical School, Massachusetts Institute of Technology, NYU Langone Medical Center and the University of Colorado, Boulder, shows that increased production of a cytokine called interleukin-17a by a subset of helper T cells (Th17) was the mechanism by which the inflammatory response in the mother led to mouse versions of ASD symptoms in the offspring: deficits in social approach behavior, abnormal communication and increases in repetitive behavior.

"Blocking the function of Th17 cells and IL-17a in the maternal womb by using antibodies and other genetic techniques completely restored normal behavior and brain structure in the affected offspring," said Jun R. Huh, PhD, an assistant professor of medicine in the division of infectious diseases and immunology at the University of Massachusetts Medical School and a corresponding author on the study.

"The study also showed that a therapeutic treatment with antibodies blocking IL-17a corrected certain behavioral abnormalities, suggesting Th17 cells, as well as the specific proteins they produce, may be candidate therapeutic targets in efforts to prevent autism in the children of susceptible mothers."

"To our knowledge, this is the first study to identify a specific population of immune cells that may have a direct role in causing behaviors linked to autism," said immunologist and another corresponding author Dan Littman, MD, PhD, the Helen L. and Martin S. Kimmel Professor of Molecular Immunology in the Department of Pathology at NYU Langone Medical Center.

Littman noted that the immune reactions in the current study linked to autism risk are the kind caused only by viral infections in the mother, and have "nothing whatsoever to do with vaccines." Some have linked childhood vaccination to autism risk despite "overwhelming scientific evidence to the contrary."

The new study centers on T lymphocytes, immune cells that react to infections by expanding into a cellular army that attacks the invading microbe at hand. A subset of T cells, Th17 cells release interleukin 17 (IL-17), a signaling protein (cytokine) that amplifies normal immune responses to fend off infections. When overactive or off target, cytokines contribute to inflammatory and autoimmune diseases like psoriasis and inflammatory bowel disease. Th17 cells supply most of a version of IL-17 called IL-17a.

Specifically, the study found that activation of Th17 cells and related IL-17a production are the core mechanisms by which inflammation in mouse mothers create behavioral abnormalities in their litters. The results in particular point to Th17 cell activation regulated by retinoid-related orphan receptor gamma t (ROR gamma t), which turns on genes that enable T cells to mature and produce IL-17a in humans and mice.

In behavioral experiments, the study authors found that exposure in the womb to IL-17a, produced in higher levels in reaction to injecting the mother with poly-I:C, created autism-like symptoms. For example, mice exposed to higher IL-17a levels in the womb had trouble telling the difference between another live mouse and a toy. They interacted with both equally, whereas normal mice spent more time socially interacting with live mice.

In terms of communication differences, mouse pups are known to cry to their mothers, but recordings revealed that offspring exposed to IL-17a inflammation vocalized abnormally. Mice exposed to this kind of immune response were also more likely to bury marbles found in their cages one after the other in a compulsive, repetitive behavior.

The research team also found that Th17-driven inflammation via IL-17a interfered with normal development of certain regions of the brain. Otherwise carefully ordered nerve cell layers became chaotic in the cortex, the part of the brain that sculpts sights and sounds into thoughts. The team focused on this feature because disorganized cortical architecture had been found in past studies of human patients with autism.

Blocking the action of Th17 cells completely restored normal structure and function to the brains of the study offspring, regardless of whether this was accomplished by treatment with anti-IL17a antibodies or by blocking the expression of ROR gamma to shut down the IL-17a gene.

"We don't know yet how these findings are correlated in humans," said Huh. "We need to find out, for example, whether Th17 cells have the same key function in human mothers as in mice, so what is needed next is a human study to monitor IL-17a levels in a large number of women, including those infected with viruses or who have autoimmune conditions, during pregnancy and correlate those levels with the diagnosis of autism spectrum disorder in children over several years."

Source:
University of Massachusetts Medical School
