Researchers find pregnancy cytokine levels impact fetal brain development and offspring behavior

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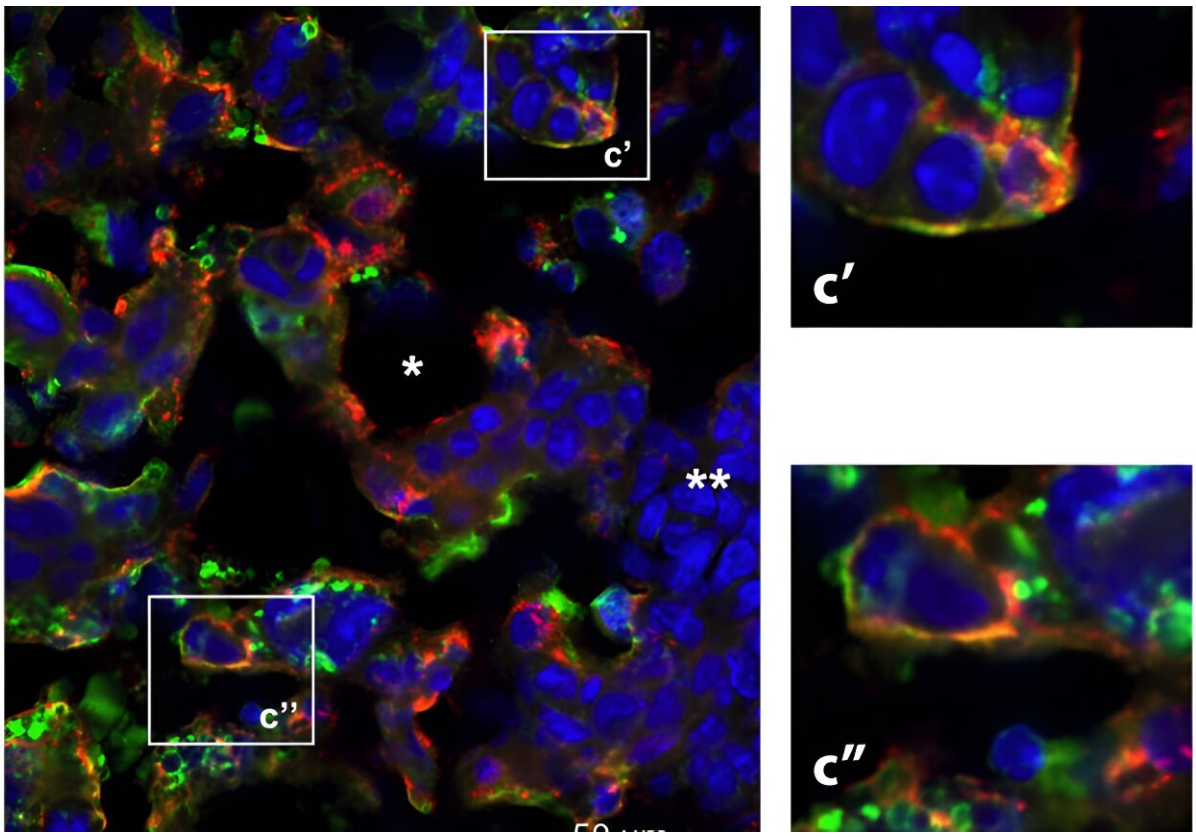

The maternal hormone-like cytokine XCL1 acts interacts with specific receptors (green) on the surface of specialized fetal placenta cells (red). c', c'' show specialized fetal cells with receptor expression (yellow). Credit: Credit: Toth Lab

Researchers at Weill Cornell Medicine have discovered in a preclinical model that cytokines, proteins that control immune response, circulating in maternal blood during pregnancy may mitigate an offspring's risk for psychiatric conditions. The findings are surprising because circulating maternal cytokines are at such low levels that they were not implicated in fetal brain development and offspring behavior before.

The study published online in *Brain, Behavior, and Immunity* on Feb 29, reported that cytokine XCL1 produced by maternal immune cells can function as a pregnancy hormone and is required for the proper development of placenta and male offspring fear behavior. These results support epidemiological studies which have long suggested a link between human maternal infection and inflammation during pregnancy and offspring developing psychiatric disorders later life.

"Using mouse models, we found that circulating XCL1 normally remained at the same low pre-pregnancy level throughout gestation except for a short rise and fall in the middle period," said corresponding author Dr. Miklos Toth, professor of pharmacology at Weill Cornell Medicine. "This temporary rise is essential for the proper development of the placenta and offspring emotional behavior."

First author Dr. Rosa Chen was a graduate student in the Toth lab during the study, which was a collaboration with Dr. Heidi Stuhlmann, acting chair of Biochemistry and also of Cell and Developmental Biology and the Harvey Klein Professor of Biomedical Sciences, Cell and Developmental Biology at Weill Cornell Medicine.

When this spike in XCL1 in maternal blood was blocked genetically or neutralized by anti-XCL1 antibodies, the researchers found increased production of factors associated with tissue damage in the fetal placenta which led to increased innate anxiety and stress reactions in male mouse offspring. The researchers also found a neuronal abnormality in the

developing brains of these offspring, specifically in the ventral hippocampus, a region that has been linked to anxiety and anxious behavior.

The immune and neuronal abnormalities observed when the cytokine spike was blocked were normalized by adulthood, suggesting that the adult anxious behavior of the offspring could be related to the early life proinflammatory state caused by the absence of elevated XCL1.

Dr. Toth will explore other chemokines that may regulate placenta development and impact offspring emotional behavior. The team plans to collaborate with researchers who have access to blood samples from pregnant women to see if the profile of XCL1, a protein also found in humans, corresponds to the observations in mouse models.

More information: Rosa J. Chen et al, The chemokine XCL1 functions as a pregnancy hormone to program offspring innate anxiety, *Brain, Behavior, and Immunity* (2024). DOI: 10.1016/j.bbi.2024.02.032

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