Immune system changes during pregnancy are precisely timed

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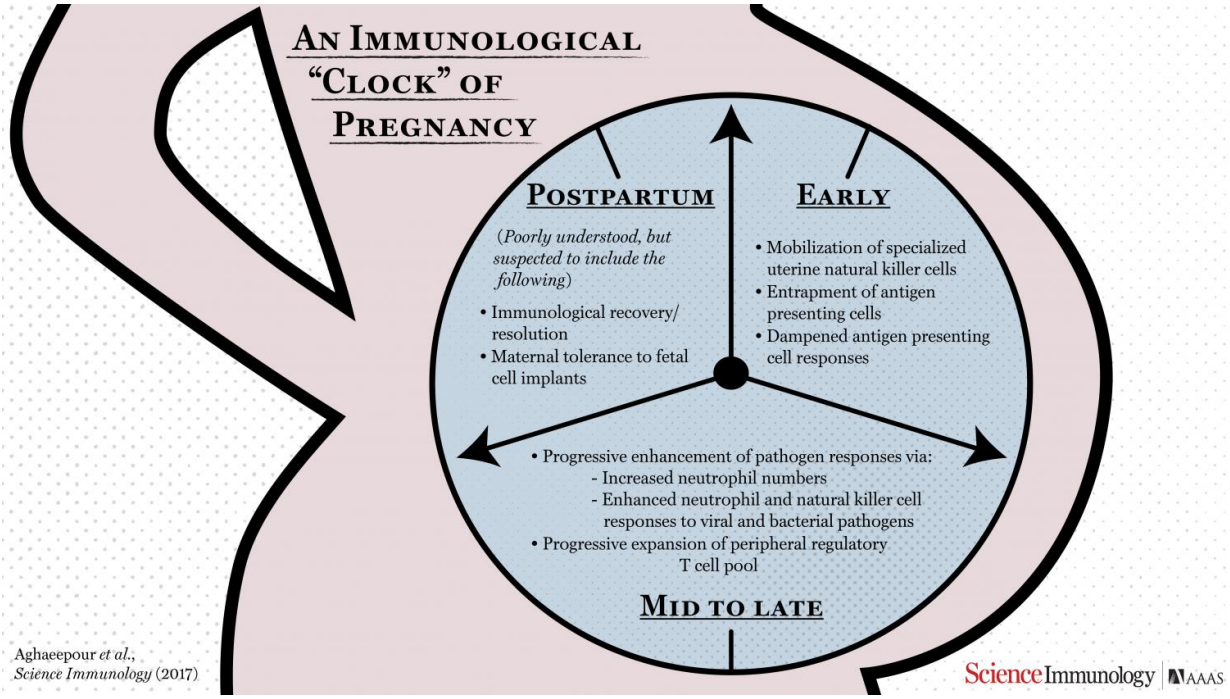


An immunological "clock" of pregnancy highlights key immune system features at certain time points during pregnancy. Credit: Carla Schaffer / AAAS

Scientists at the Stanford University School of Medicine have completed the first-ever characterization of the meticulously timed immune system changes in women that occur during pregnancy.

The findings, which will be published Sept. 1 in *Science Immunology*,

reveal that there is an immune clock of pregnancy and suggest it may help doctors predict preterm birth.

"Pregnancy is a unique immunological state. We found that the timing of immune system changes follows a precise and predictable pattern in normal pregnancy," said the study's senior author, Brice Gaudilliere, MD, PhD, assistant professor of anesthesiology, perioperative and pain medicine.

Although physicians have long known that the expectant mother's immune system adjusts to prevent her body from rejecting the fetus, no one had investigated the full scope of these changes, nor asked if their timing was tightly controlled. "Ultimately, we want to be able to ask, 'Does your immune clock of pregnancy run too slow or too fast?'" said Gaudilliere.

The new research comes from the March of Dimes Prematurity Research Center at Stanford University, which aims to understand why preterm births happen and how they could be prevented. Nearly 10 percent of U.S. infants are born prematurely, arriving three or more weeks early, but physicians lack a reliable way to predict premature deliveries.

"It's really exciting that an immunological clock of pregnancy exists," said the study's lead author, Nima Aghaeepour, PhD, instructor in anesthesiology, perioperative and pain medicine. "Now that we have a reference for normal development of the immune system throughout pregnancy, we can use that as a baseline for future studies to understand when someone's immune system is not adapting to pregnancy the way we would expect."

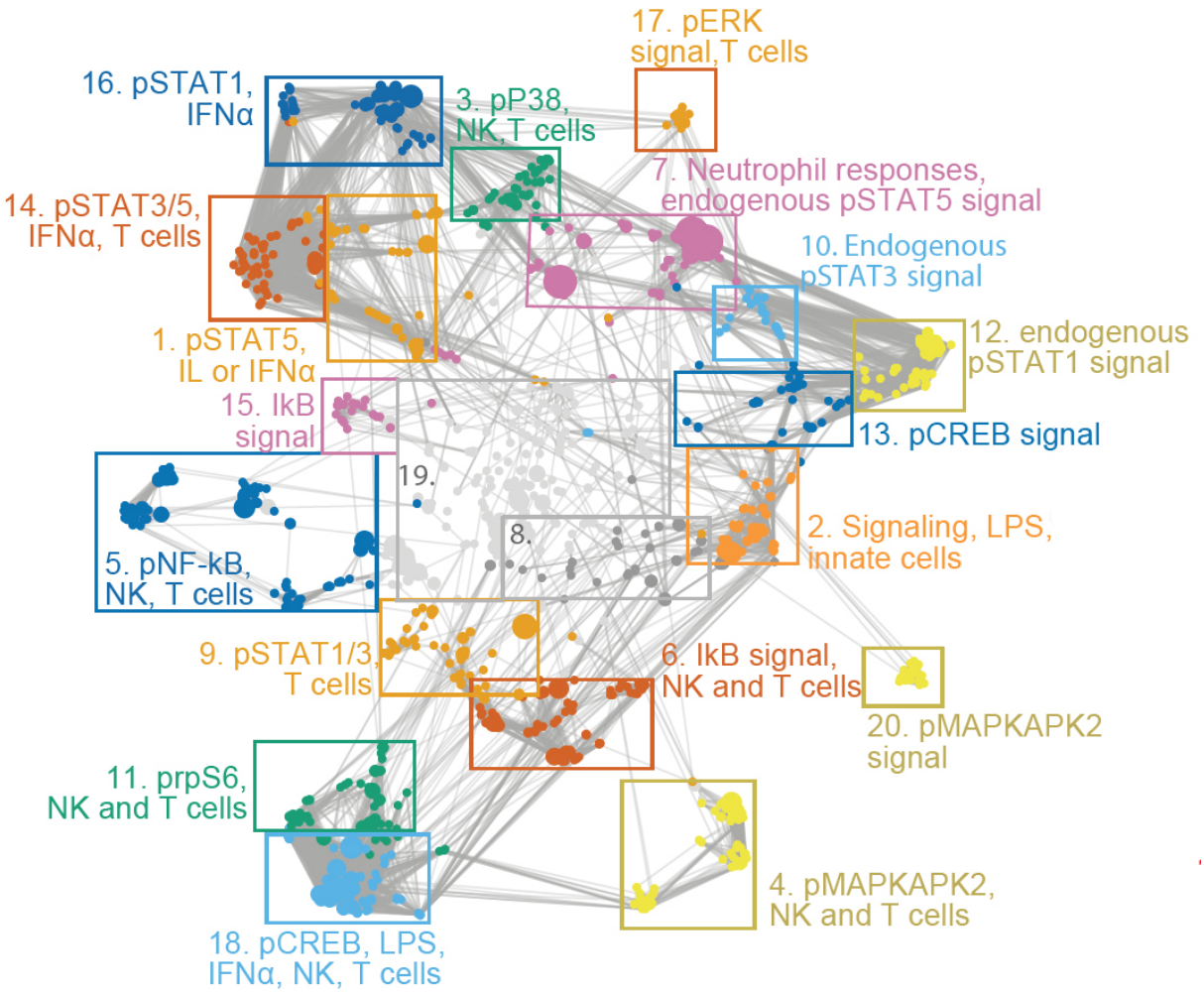
Prior research at Stanford and elsewhere suggested that inflammatory immune responses may help trigger early labor. If scientists identify an

immune signature of impending preterm birth, they should be able to design a blood test to detect it.

The study used blood samples collected from 18 women who had full-term pregnancies. Each woman gave four blood samples—one during each of the three trimesters of pregnancy and one six weeks after delivery. Samples from an additional group of 10 women with full-term pregnancies were used to validate the findings.

How each immune cell experiences pregnancy

The researchers used mass cytometry, a technique developed at Stanford, to simultaneously measure up to 50 properties of each immune cell in the blood samples. They counted the types of immune cells, assessed what signaling pathways were most active in each cell, and determined how the cells reacted to being stimulated with compounds that mimic infection with viruses and bacteria.



Aghaeepour et al.'s analysis revealed entire cellular programs, rather than isolated mechanisms, that characterized the chronological progression of immune adaptations over the entire course of pregnancy. Credit: Aghaeepour et al., *Sci. Immunol*. 2, eaan2946 (2017)

With an advanced statistical modeling technique, introduced for the first time in this study, the scientists then described in detail how the immune system changes throughout pregnancy.

"This algorithm is telling us how specific immune cell types are

experiencing pregnancy," Gaudilliere said.

Instead of grouping the women's blood samples by trimester for analysis, their model treated gestational age as a continuous variable, allowing the researchers to account for the exact time during pregnancy at which each sample was taken. The mathematical model also incorporated knowledge from the existing scientific literature of how immune cells behave in nonpregnant individuals to help determine which findings were most likely to be important. The model improved understanding of the immune system much as mapping software that knows which streets are one-way gives better driving directions. "If there are several models that are statistically equivalent, we are interested in the model that is most consistent with our existing knowledge of immunology," said Aghaeepour.

Hopes of finding 'sweet spot'

The study confirmed immune features of pregnancy that were already known. For instance, the scientists saw that natural killer cells and neutrophils have enhanced action during pregnancy. The researchers also uncovered several previously unappreciated features of how the immune system changes, such as the finding that activity of the STAT5 signaling pathway in CD4+T cells progressively increases throughout pregnancy on a precise schedule, ultimately reaching levels much higher than in nonpregnant individuals. The STAT5 pathway is involved in helping another group of immune cells, regulatory T cells, to differentiate. Interestingly, prior research in animals has indicated that regulatory T cells are important for maintaining pregnancy.

The next step will be to conduct similar research using blood samples from women who deliver their babies prematurely to see where their trajectories of immune function differ from normal.

"We're especially interested in understanding more precisely what is happening very early and very late in pregnancy," Gaudilliere said. "We'd like to see if there is really a switch we can catch, a sweet spot where deviation from the norm would be maximal with pathology."

"The immune system does not act in isolation, and we're now very interested in profiling its interplay with other aspects of mothers' biology, such as their genetics, metabolism and the body's microbial communities to come up with a holistic biological clock of pregnancy," Aghaeepour added.

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

More information: N. Aghaeepour el al., "An immune clock of human pregnancy," *Science Immunology* (2017). immunology.sciencemag.org/look … 6/sciimmunol.aan2946

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