Specialized cells teach the mother's immune system to maintain a healthy pregnancy

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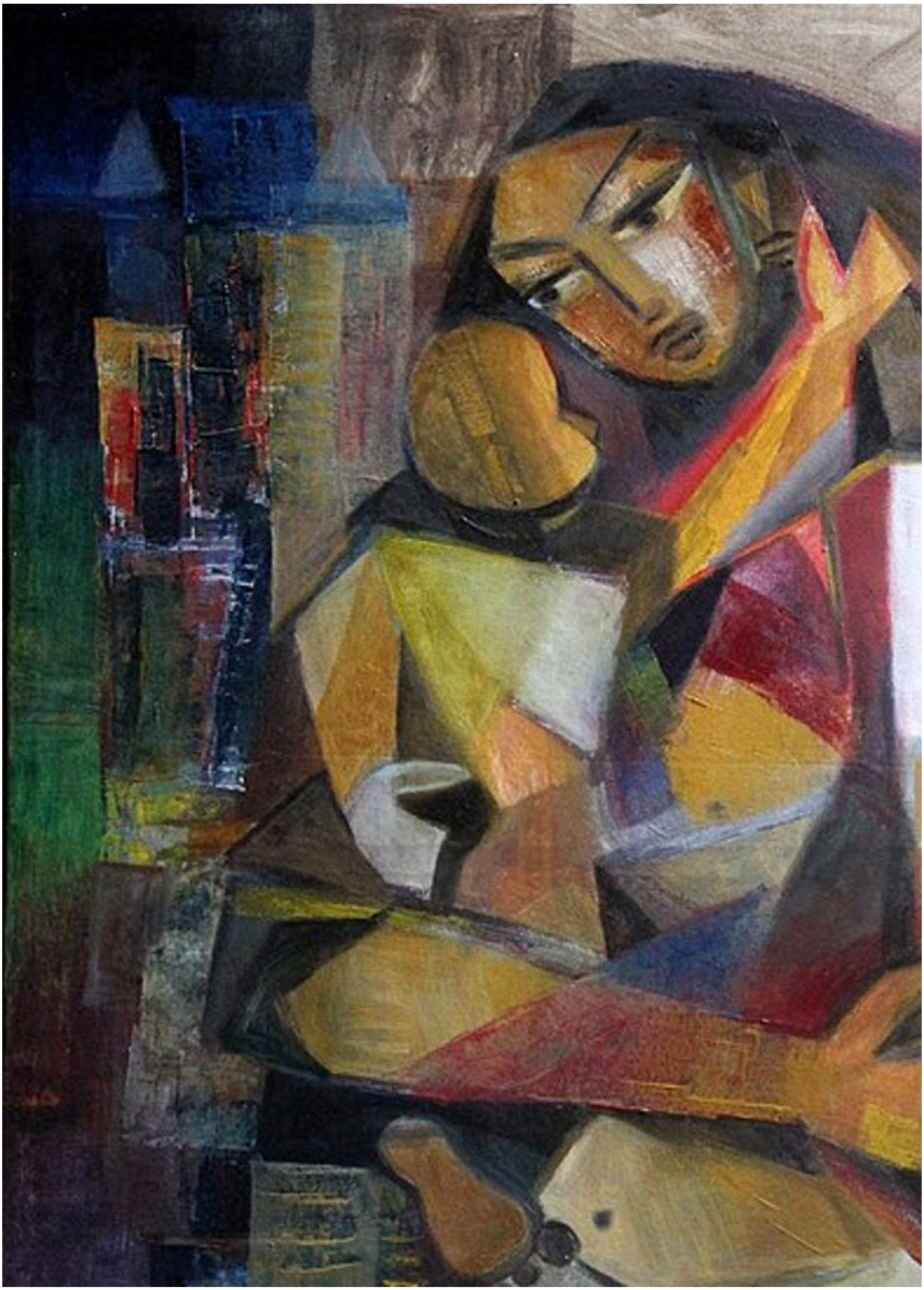

During pregnancy, the body's specialized immune cells must learn to recognize the fetus as part of the self so that they don't attack it. Credit: Raja Segar via Wikimedia Commons, CC BY-SA

During pregnancy, immune educator cells teach the mother's immune system to recognize the developing fetus as part of her "self," protecting it from being attacked as something "other," according to our new study published in *Science Immunology*.

The immune system normally protects the body from such invaders as infections and cancers. But how exactly does it know what to attack and what to leave alone? How does it learn not to target one's own organs or tissues, or, in the case of pregnancy, the developing fetus?

A fetus shares a blood supply and immune system with its mother, which presents unique challenges—the fetus is genetically different from the mother, and it also develops specialized organs like the placenta that might seem foreign to the mother's immune system. How her system learns not to attack the fetus and placenta is incredibly important to understanding pregnancy and its common complications, like miscarriage.

Scientists have sought to understand a more basic version of this question for years: How does the immune system generally learn what to attack and what not to attack?

In a process known as immune self-education, which happens in an organ called the thymus, specialized "educator cells" teach developing immune cells what not to attack by showing off a diverse array of the body's own proteins. Essentially, this process teaches immune cells what

constitutes "self." These educator cells require a unique protein called the autoimmune regulator, or Aire, to teach the complete curriculum of the body's own proteins, and mutations in Aire lead to a devastating autoimmune disease.

Previously, we and others discovered a new class of educator cells living outside of the thymus, predominantly in the lymph nodes and spleen, that make this same Aire protein. We called them extrathymic Aire-expressing cells, or eTACs, and suspected they might serve as a kind of "continuing education" for the immune system. Our newest discovery is that eTACs are essential for protecting pregnancy by teaching the mother's immune system not to attack the fetus and placenta as something foreign. This study, done in mice that we engineered to be able to delete Aire-expressing cells, shows that in the absence of eTACs, the mother's immune system gets overactivated and attacks the pregnancy.

Pregnancy complications like miscarriage are common, but the cause is frequently a mystery. Understanding how the immune system works to protect pregnancy may help scientists and doctors better identify, and hopefully prevent or treat, more of these pregnancy complications.

More broadly, understanding what role extrathymic Aire-expressing cells play in immune self-education may have implications for a wide range of diseases. While the thymus and its educator cells shrink and die off during normal development, eTACs circulate around the body for the duration of one's life. If researchers can understand their biology and function, physicians may be able to treat autoimmune diseases like juvenile diabetes, cancers that evade immune detection and organ transplants rejected by the immune system. It would be groundbreaking, for example, to be able to rewrite the curriculum of the immune system to accept a new organ in the same way it accepts a fetus.

Our initial study showed that eTACs are essential for maintaining a healthy pregnancy by keeping the mother's immune system in check, but exactly how they do this remains a mystery. Also unknown is the precise role that the Aire protein plays in the process and in these cells. We also don't know yet whether eTACs play a role in other diseases, such as cancer and juvenile diabetes, that also involve self-recognition by the immune system. We hope that by understanding the fundamentals of how the immune system learns, we may be able to use this knowledge to fine-tune immune self-education to ultimately treat a wide range of diseases.

More information: Eva Gillis-Buck et al, Extrathymic Aire-expressing cells support maternal-fetal tolerance, *Science Immunology* (2021). DOI: 10.1126/sciimmunol.abf1968

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