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From: [REDACTED]
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<http://www.pnas.org/content/107/20/9299.full.pdf>

Here's a short...

Tolerating a Fetus

Your immune system recognizes cells in your body that aren't yours, hunts them down, and kills them. So how does a fetus survive? Half of its genes and all of its tissues are unlike mom's, yet the body does not attack this invader.

Caltech biologists have discovered that a particular type of immune cell—produced in response to specific fetal antigens, proteins that stimulate the immune system—allows "pregnancy tolerance," as it's called.

"Our finding that specific T regulatory cells protect the mother is a step to learning how the mother avoids rejection of her fetus. This central biological mechanism is important for the health of both the fetus and the mother," says David Baltimore, the Millikan Professor of Biology, and recipient of the 1975 Nobel Prize in Physiology or Medicine.

Scientists had long been "hinting around at the idea that the mother's immune system makes tolerance possible," says Daniel Kahn, a visiting associate in biology at Caltech, and an assistant professor of maternal-fetal medicine at the UCLA. What they didn't have were the details of this tolerance—or proof that it was immune-related.

Now they do. Baltimore and Kahn selectively destroyed the T regulatory cells in a strain of mice bred so that all the males—including male fetuses—carry on their cells' surfaces a protein known as a "minor transplantation antigen." Female mice lack this antigen.

Normally, pregnancy tolerance would kick in and protect the male fetuses from any maternal repercussions. So if the T regulatory cells provided the shield, their destruction would give the immune system free rein to go after the antigen-laden males—and only the males.

And indeed, fewer male fetuses survived to birth. Those that did were of significantly lower birthweight, presumably because of the inflammation caused by the mother's immune response to that single antigen.

The scientists found that pregnancy tolerance "develops actively as a consequence of pregnancy," says Kahn. "The mice are not born with it." Indeed, virgin mice showed no signs of these pregnancy-specific T regulatory cells. Conversely, the cells were found in larger numbers in mice that had given birth to male babies, with the level of T regulatory cells increasing with the number of male births.

The next step, Kahn adds, is to look at T regulatory cells and their role in pregnancy tolerance in humans—a line of research that may lead to insights into such pregnancy-related conditions as preeclampsia, in which high blood pressure and other symptoms develop in the second half of pregnancy. Preeclampsia is a major cause of maternal mortality around the world.

"There's a lot to be learned," he says. "Pregnancy is often ignored in research because it's usually successful, and because—from an immunologic standpoint—it has such complexity. Until now, it's been difficult to get a handle on how the immunology of pregnancy really works."

The work is described in an article by Baltimore and Kahn in the May 18 issue of the *Proceedings of the National Academy of Sciences*. The research was supported in part by a grant from the Skirball Foundation.

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