Researchers Show How Active Immune Tolerance Makes Pregnancy Possible

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(PhysOrg.com) -- The concept of pregnancy makes no sense -- at least not from an immunological point of view. After all, a fetus, carrying half of its father's genome, is biologically distinct from its mother. The fetus is thus made of cells and tissues that are very much not "self" -- and not-self is precisely what the immune system is meant to search out and destroy.

Women's bodies manage to ignore this contradiction in the vast majority of cases, making pregnancy possible. Similarly, scientists have generally paid little attention to this phenomenon—called "pregnancy tolerance"—and its biological details.

Now, a pair of scientists from the California Institute of Technology (Caltech) have shown that females actively produce a particular type of immune cell in response to specific fetal antigens—immune-stimulating proteins—and that this response allows pregnancy to continue without the fetus being rejected by the mother's body.

Their findings were detailed in a recent issue of the Proceedings of the National Academy of Sciences *(PNAS)*.

“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, Caltech's Robert Andrews Millikan Professor of Biology, recipient of the 1975 Nobel Prize in Physiology or

Medicine, and the principal investigator on the research.

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

Now they do. To pin down those details, the two scientists began looking at the immune system's T regulatory cells (Tregs) in a strain of inbred mice that are all genetically identical—except for one seemingly tiny detail. Male mice—including male fetuses—carry on their cells' surfaces a protein known as a "minor transplantation antigen." Female mice lack this antigen.

Under normal circumstances, this antigen's existence isn't a problem for the male fetuses because the pregnancy tolerance phenomenon kicks in and protects them from any maternal immune repercussions.

To demonstrate the role of Tregs, Baltimore and Kahn used a drug to selectively target and destroy the cells. If the Tregs were indeed the source of pregnancy tolerance, they reasoned, their destruction would give the immune system free rein to go after the antigen-laden fetuses.

"In this case," says Kahn, "we knew the only possible immune response would be against the males—that the males would be at risk."

Indeed they were. When Baltimore and Kahn looked at the offspring of mice who'd been treated with the toxin, they found that fewer of the male fetuses survived to birth; those males that did survive were of significantly lower birthweight, presumably because of the inflammation caused by the mother's immune response to that single antigen.

"These T cells are functioning in an antigen-specific manner," Kahn notes. "In other words, their function requires the presence of the specific fetal antigens."

In their studies of these animals, the scientists also 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 Treg cells. Conversely, the cells were found in larger numbers in those individual mice that had given birth to more male babies, with the level of Treg cells increasing with the number of male births.

The next step, Kahn adds, is to look at Tregs and their role in pregnancy tolerance in humans—a line of research that may lead to new 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 grab a handle on how the immunology of pregnancy really works."

The work described in the *PNAS* article, "Pregnancy induces a fetal antigen-specific maternal T regulatory cell response that contributes to tolerance," was supported in part by a research grant from the Skirball Foundation. Kahn is supported by the National Institutes of Health's Building Interdisciplinary Research Careers in Women's Health Center at UCLA.