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Human Fetal Immune System Arises from Entirely Different Source Than Adult Immune System

UCSF researchers have shown for the first time that the human fetal immune system arises from an entirely different source than the adult immune system, and is more likely to tolerate than fight foreign substances in its environment.

The finding could lead to a better understanding of how newborns respond to both infections and vaccines, and may explain such conundrums as why many infants of HIV-positive mothers are not infected with the disease before birth, the researchers said.

It also could help scientists better understand how childhood allergies develop, as well as how to manage adult organ transplants, the researchers said. The findings are described in the Dec. 17 issue of Science.

Until now, the fetal and infant immune system had been thought to be simply an immature form of the adult system, one that responds differently because of a lack of exposure to immune threats from the environment. The new research has unveiled an entirely different immune system in the fetus at mid-term that is derived from a completely different set of stem cells than the adult system.

"In the fetus, we found that there is an immune system whose job it is to teach the fetus to be tolerant of everything it sees, including its mother and its own organs," said Joseph M. McCune, MD, Ph.D, a professor in the UCSF Division of Experimental Medicine who is a co-senior author on the paper. "After birth, a new immune system arises from a different stem cell that instead has the job of fighting everything foreign."

The team previously had discovered that fetal immune systems are highly tolerant of cells foreign to their own bodies and hypothesized that this prevented fetuses from rejecting their mothers' cells during pregnancy and from rejecting their own organs as they develop.

The adult immune system, by contrast, is programmed to attack anything it considers "other," which allows the body to fight off infection, but also causes it to reject transplanted organs.

"The adult immune system's typical role is to see something foreign and to respond by attacking and getting rid of it. The fetal system was thought in the past to fail to 'see' those threats, because it didn't respond to them," said Jeff E. Mold, first author on the paper and a postdoctoral fellow in the McCune laboratory. "What we found is that these fetal immune cells are highly prone to 'seeing' something foreign, but instead of attacking it, they allow the fetus to tolerate it."

The previous studies attributed this tolerance at least in part to the extremely high percentage of "regulatory T cells"- those cells that provoke a tolerant response -- in the fetal immune system. At mid-term, fetuses have roughly three times the frequency of regulatory T cells as newborns or adults, the research found.

The team set out to assess whether fetal immune cells were more likely to become regulatory T cells. They purified so-called naïve T cells -- new cells never exposed to environmental assault -- from mid-term fetuses and adults, and then exposed them to foreign cells. In a normal adult immune system, that would provoke an immune attack response.

They found that 70 percent of the fetal cells were activated by that exposure, compared to only 10 percent of the adult cells, refuting the notion that fetal cells don't recognize outsiders. But of those cells that responded, twice as many of the fetal cells turned into regulatory T cells, showing that these cells are both more sensitive to stimulation and more

likely to respond with tolerance, Mold said.

Researchers then sorted the cells by gene expression, expecting to see similar expression of genes in the two cell groups. In fact, they were vastly different, with thousands of genes diverging from the two cell lines. When they used blood-producing stem cells to generate new cell lines from the two groups, the same divergence occurred.

"We realized they there are in fact two blood-producing stem cells, one in the fetus that gives rise to T cells that are tolerant and another in the adult that produces T cells that attack," Mold said.

Why that occurs, and why the immune system appears to switch over to the adult version sometime in the third trimester, remains unknown, McCune said. Further studies will attempt to determine precisely when that occurs and why, as well as whether infants are born with a range of proportions of fetal and adult immune systems -- information that could change the way we vaccinate newborns or treat them for such diseases as HIV.

Co-authors of the study include Trevor D. Burt, Jose M. Rivera, Sofiya Galkina and Co-senior Author Cheryl A. Stoddart, all from the UCSF Department of Medicine, Division of Experimental Medicine; Jakob Michaelsson, from the Center for Infectious Medicine, Karlinska Institutet, Stockholm, Sweden; and Shivkumar Venkatasubrahmanyam and Kenneth Weinberg, of the Center for Biomedical Informatics Research and Division of Hematology/Oncology, respectively, at Stanford University, Palo Alto, Calif. Burt also is affiliated with the UCSF Division of Neonatology in the Department of Pediatrics.

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J. E. Mold, S. Venkatasubrahmanyam, T. D. Burt, J. Michaelsson, J. M. Rivera, S. A. Galkina, K. Weinberg, C. A. Stoddart, J. M. McCune. Fetal and Adult Hematopoietic Stem Cells Give Rise to Distinct T Cell Lineages in Humans. Science, 2010; 330 (6011): 1695 DOI: 10.1126/science.1196509