The New York Times

February 3, 2009

Transfer of Mother's Cells Molds Baby's Immunity

By AMANDA SCHAFFER

Researchers have long wondered how pregnant women might shape their fetuses' development — by protecting them against later disease, perhaps, or instilling an appreciation of Mozart.

Now a group in California has discovered a surprising new mechanism by which women train their fetuses' budding immune systems: the mother's cells slip across the placenta, enter the fetus's body and teach it to treat these cells as its own.

A crucial task of the developing immune system is to learn to distinguish between foreign substances and the self. It is tricky: the system must respond to outside threats but not overreact to harmless stimuli or the body's own tissues.

The new findings show "how Mom is helping to tune that whole system early on," said William J. Burlingham, an immunologist at the University of Wisconsin, who is not connected with the research. "It's a major advance, very new and very exciting."

The work could have relevance to research on topics as diverse as organ transplantation, mother-to-child transmission of H.I.V. and autoimmune disorders like Type 1 diabetes.

"It points the way to a huge range of biologically significant questions that are worth exploring," Dr. Burlingham said.

The researchers, based at the University of California, San Francisco, worked with lymph nodes and spleens from aborted second-trimester fetuses. They also drew blood from the women who had been carrying these fetuses to test for specific immune responses.

The team examined 18 samples of fetal lymph nodes and found evidence of maternal cells in 15 of them.

Researchers have known for decades that some maternal cells cross the placenta and can be observed in fetal tissue. But experts said the new work suggested a strikingly high frequency of maternal cells.

"It tells us that we need to pay more attention to what these cells are doing," said Dr. J. Lee Nelson, an immunologist at the Fred Hutchinson Research Center in Seattle, who conducted early research suggesting that maternal cells may persist in the tissue of normal adults.

The San Francisco team also observed that regulatory T cells, a particular type of immune cell, were present in large numbers in the fetal lymph nodes. Regulatory T cells typically act to suppress immune responses. In a pregnant woman, for instance, these cells may help to prevent the immune system from treating the fetus as foreign and attacking it.

The scientists wondered whether a symmetrical mechanism might be at work in the fetus. "We wanted to get at what was inducing these cells to proliferate and what role they were playing specifically in fetal tissue," said Jeff E. Mold, an immunology graduate student at U.C.S.F.

The group was able to demonstrate that cells from the mother directly cause fetal tissue to produce more regulatory T cells. These, in turn, help keep the fetal immune system from attacking the mother's cells.

The fetus is genetically distinct from the mother and the father, since some of its DNA comes from each parent. This means that its immune system could reject cells from its mother as foreign, since these cells have some surface characteristics that were not inherited. The current work may help to explain why that does not seem to happen in the course of a normal pregnancy.

"We found a specific mechanism for how the mother's cells induce the fetal immune system to be more tolerant," said Mr. Mold, who was the first author of the paper, which appeared in Science on Dec. 5.

Other experts say the findings could have important implications for work on transplants.

When patients receive transplanted organs, they generally have to take drugs to suppress their immune system and keep it from attacking the foreign tissue. But these drugs may be associated with greater susceptibility to kidney problems, infection and bone weakness, said Dr. Burlingham, of Wisconsin.

"We would like to find ways of transplanting tissue without creating lifelong dependence on these drugs," he said. "That might be possible if researchers took the immune profiles of patients' mothers into account to a great degree when selecting organs for transplant."

As early as the 1980s, scientists in the Netherlands observed that many patients who were waiting to receive kidney transplants and who had formed antibodies against most potential donors did not react against their own mothers' white blood cells. That suggested that during fetal development, a process was allowing the fetus to tolerate tissue with motherlike surface molecules.

The new research explains "precisely how that works," said Dr. Jon J. van Rood, a professor of internal medicine at the University of Leiden who conducted the original research. By homing in on regulatory T cells in fetal lymph nodes, "they found the crucial clue."

The discovery may also be relevant to the study of mother-to-child transmission of infectious disease.

When pregnant women are infected with H.I.V., for instance, they often do not pass the disease to the fetus, said Dr. Joseph M. McCune, the immunologist who led the U.C.S.F. group. Fewer than half of all babies born to H.I.V.-positive mothers are infected themselves, and of those, only a small fraction are infected in the womb, he said.

If H.I.V. is crossing the placenta in the same way as the mother's cells and if the fetus is also suppressing an immune response against the virus, it is surprising that more fetuses are not infected, he said.

Dr. McCune said he wondered whether the same mechanism that prevents the fetus from attacking its mother's cells might also help to protect it from infection. And he wonders whether tolerance could be central to both processes.

"These are some of the major questions we're interested in now," he said.

The new finding may also bolster wide-ranging work on autoimmune diseases.

Researchers already know that during development, the fetal immune system can kill off specific populations of immune cells that have the capacity to attack the body's own tissue. But the new work suggests another mechanism for avoiding unwanted attacks on the self. "We now have another handle on how the fetus may learn to distinguish between self and nonself," Dr. McCune said. If problems with regulatory T cell mechanisms occur in utero, that might set the stage for some autoimmune disorders, he said.

In the long run, he added, by manipulating patients' regulatory T cells — perhaps by modifying the number or activity of these cells — scientists may someday develop new therapies for these diseases.

Research groups around the world are studying the role of regulatory T cells in a wide range of basic processes and disease models. "It's an explosive area," Dr. Burlingham said.

And now, he said, it appears that critical processes are set in motion because early on, "we must all learn to tolerate our mothers."