EVOLUTION

Tamed immune reaction aids pregnancy

Evolutionary studies show how dialing back inflammation allows embryo implantation

By **Elizabeth Pennisi**,
in San Francisco, California

The riskiest moment in any human pregnancy is arguably when the fertilized egg attaches to the womb wall and tries to establish a lifeline between embryo and mother. About half of in vitro pregnancies fail during this implantation stage, and many natural pregnancies end then as well. Now, researchers comparing pregnancy in opossums and several other mammals have shown how precise control of an immune process, inflammation, is critical to success or failure.

In work reported here this month at the annual meeting of the Society for Integrative and Comparative Biology, a Yale University team led by evolutionary developmental biologist Günter Wagner concluded that human and other so-called placental mammals have tweaked an ancient inflammatory process to enable embryos to implant and persist in the womb. Placental mammals—named for the mass of tissue in the uterus that serves as the interface between mother and fetus—have specialized uterine cells that suppress the release of a key immune-stimulating molecule. This suppression may help delay the rejection of the embryo until it's ready to be born, Arun Chavan, a Yale graduate student in Wagner's lab, told the meeting.

An unrestrained inflammatory response triggers the birth of opossum young early in their development.

Beyond solving a key mystery about pregnancy, the work could also point to treatments for infertility and miscarriage, says Tom Stewart, an evolutionary developmental biologist at the University of Chicago in Illinois. "The more we understand about pregnancy in other species, the more likely it is that we can treat medical issues that arise during human pregnancy."

Researchers have always puzzled over why the mother allows an embryo, which is basically a parasite, to settle in and grow. Yet implantation "was a critical first step in evolving pregnancy as humans experience it," says Julia Bowsher, an integrative biologist at North Dakota State University in Fargo.

This seeming paradox is even more perplexing because although a mother's inflammatory reaction to this "parasite" is the biggest threat to pregnancy, it also seems necessary for the pregnancy to be successful, Wagner, Chavan, and Yale postdoc Oliver Griffith pointed out last year. A woman's chance of implantation actually increases if her uterus has suffered mild trauma, for example, from a uterine biopsy as part of an in vitro fertilization (IVF) procedure. Studies have shown that the IVF embryo is more likely to settle in, particularly at the biopsy site. Furthermore, an immune "rejection" response helps create the contractions necessary for a baby's birth. Yet in between implantation and birth, the immune system is held in check, allowing the fetus to thrive.

To understand the evolutionary basis for this interlude, Griffith recently led a study of gene activity in a marsupial, the gray short-tailed opossum (*Monodelphis domestica*). Marsupials have very short pregnancies. Early opossum embryos develop for about 12 days, enclosed as shelled eggs in the womb. They then shed their shells and try to attach to the uterine wall, activating placenta-promoting genes. But after about 2 days, the mother's immune system "rejects" the embryos, causing the birth of a litter that is still very immature compared with newborn placental mammals.

Griffith sampled opossum gene activity before pregnancy, during the egg-shell stage, and after implantation. The analysis revealed the array of immune system signaling molecules and steroid hormones taking part in the immune attack on the embryo. The gene activity also pointed to a role for immune cells such as neutrophils, which launch a full-fledged inflammatory reaction that includes molecules that stimulate contractions of the uterus. The timing and makeup of this response largely mirror what is seen in implantation in placental mammals, indicating that the process evolved in the common ancestor of placental and marsupial mammals, Griffith and colleagues reported in the 26 July 2017 issue of the *Proceedings of the National Academy of Sciences*.

But later in evolution, placental mammals apparently dialed back that inflammation to allow extended gestation. To find out how, Chavan compared implantation in the opossum with that in a range of placental mammals: rabbits, armadillos, and hyraxes, a 3-kilogram rodentlike mammal that's closely related to elephants. Based on studies of gene activity and immune cells, he found that these mammals have "domesticated" implantation's inflammatory response. At the implantation site, blood vessels proliferate in the uterine wall—the same hallmark of inflammation seen in the opossum—but the signaling molecule IL-17, which recruits neutrophils, is missing, Chavan reported at the meeting.

Specialized cells called decidual cells seem to be responsible, he found. These cells form in the uterine lining early in pregnancy and, in many placental mammals, disappear right after implantation. Chavan wondered whether these cells might have evolved to switch the inflammatory response into low gear. Supporting that notion, he found in tissue studies that secretions of those cells could keep immune cells from making IL-17.

"If that switch doesn't happen, there are miscarriages," says Gil Mor, a reproductive immunologist at Yale who was not involved with the work. "Understanding the evolution of decidual cells will be extremely helpful to those of us studying the nitty-gritty" of pregnancy. ■

PHOTO: OLIVER GRIFFITH

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