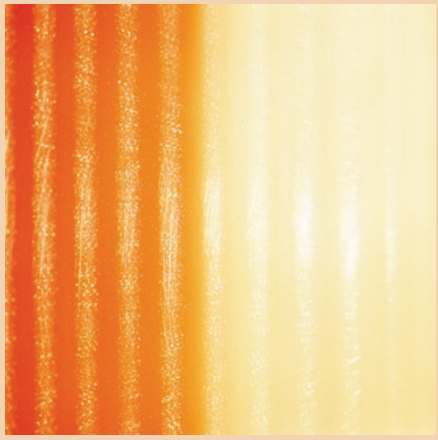
Growing gonads

Gonadotropin-releasing hormone (GnRH) deficiency leads to idiopathic hypogonadotropic hypogonadism (IHH), a disorder characterized by decreased gonad size and abnormal sexual development. IHH has been linked to mutations in several genes, but they account for only about 30% of IHH cases. In 2007, Nelly Pitteloud and her colleagues added prokineticin-2 (*PROK2*) to the list of genes that are associated with this disorder (*Proc. Natl. Acad. Sci. USA* **104**, 17447–17452; 2007).

The authors identified a mutation in the *PROK2* gene in a large family with three affected siblings and related their phenotypes to those in *Prok2*-deficient mice—abnormalities in the olfactory and reproductive systems. The affected individuals (two brothers and their sister) were all homozygous for a *PROK2* mutation that results in a premature stop codon. Expressing this mutant gene in cells resulted in a protein with no activity at its receptor.

Interestingly, the same genotype resulted in slightly different phenotypes between the affected siblings: whereas all had phenotypes associated with sexual immaturity, the two brothers had a defective sense of smell, whereas the sister did not. This link between the olfactory and the GnRH systems is consistent with the key role of the *PROK2* gene in their normal development.—*EC*

Gradients at the follicle



The ovarian follicle is comprised of an oocyte surrounded by a layer of hormone-producing granulosa cells. As the follicle expands in size and the granulosa cells increase in number, this cellular milieu becomes quite complex. In particular, the granulosa cells segregate into mural cells, which form the wall of the expanding follicle, and cumulus cells, which continue to surround the egg and help it burst from the follicle upon ovulation.

What signaling pathway is responsible for this segregation? In 2007, Francisco Diaz and his colleagues found that SMAD2 is crucial for this process (*J. Cell Sci.* 120, 1330–1340; 2007). The team showed that there is a radial gradient of follicle-stimulating hormone (FSH) signaling from the outside to the inside within the follicle, which activates mural-specific transcripts while repressing cumulus-specific transcripts. At the same time, there is a gradient running in the opposite direction, which relies on an oocyte-derived factor to compete with the FSH gradient, promoting cumulus-specific and inhibiting mural-specific transcription.

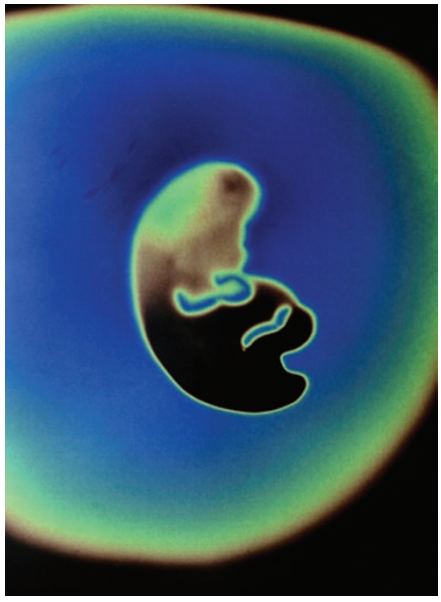
Diaz and his colleagues went on to show that the outward gradient depends on the activity of the transcription factor SMAD2, but future studies will be needed to establish the nature of the mysterious oocyte-derived factor and the signaling pathways that mediate the effect of FSH.—*RL*

Tolerance through regulatory T cells

A developing fetus needs to evade attack by the maternal immune system. In 2004, Varuna Aluvihare and his colleagues showed that changes to the maternal immune system are not restricted to the fetal-maternal interface: pregnancy elicits a systemic expansion of regulatory T cells, and these cells dampen harmful T cell responses directed against the fetus (*Nat. Immunol.* **5**, 266–271; 2004).

The authors found that pregnant C57BL/6 mice that were mated to allogenic CBA males or syngenic C57BL/6 males had higher proportions of $CD4^+CD25^+$ T cells than their nonpregnant counterparts. This population of cells constituted around 30% of uterine $CD4^+$ T cells. Likewise, mRNA levels of FoxP3—a marker for regulatory T cells—were 1,000-fold higher in the uterine tissue from pregnant female mice than in nonpregnant age-matched females.

The regulatory T cells seem to protect the fetus from effector T cells directed against paternally derived alloantigens, as the authors showed with an adoptive transfer experiment. Specifically, BALB/c nude mice (which lack T cells) receiving T cells depleted of the $CD25^+$ population failed to sustain normal pregnancy when mated to allogenic C57BL/6 males. If the mice were mated instead to syngenic BALB/c males, normal pregnancies were observed.—*CT*



p53 is pro-pregnancy

p53 is a well known tumor suppressor, but Wenwei Hu *et al.* showed in 2007 that this molecule also has an important role in maternal reproduction in mice (*Nature* **450**, 721–724; 2007).

Noting that pregnancy rates and litter sizes were reduced in crosses with $Tp53^{-/-}$ female mice, Hu *et al.* sought a p53 target that might explain its importance in reproduction. They found that p53 regulated transcription of the gene encoding leukemia inhibitory factor (LIF), a molecule that is required for blastocyst implantation. In their experiments with wild-type mice, uterine *Lif* expression increased coincident with the timing of implantation. In $Tp53^{-/-}$ mice, this increase failed to occur, and blastocyst implantation was impaired. Injection of LIF rescued the implantation defect, although 30% of the pups had developmental abnormalities.

Implantation problems are a frequent cause of the failure of assisted reproduction techniques in humans and have recently been associated with a polymorphism in *Tp53* that reduces p53 protein activity. The findings by Hu *et al.* provide a possible explanation for how p53 may influence human fertility.—*AF*

The enemy within

The pathogenesis of preeclampsia, a condition during pregnancy that can lead to sudden seizures and even death, is poorly understood. A study from Yang Xia and her colleagues published this year provided strong evidence that autoantibodies may be at the root of this disease (*Nat. Med.* **14**, 855–862; 2008).

Previous studies had shown that women with preeclampsia harbor autoantibodies—termed AT1-AAs—that bind and activate the angiotensin II receptor type 1a. Inappropriate activation of this receptor would explain many of the symptoms of preeclampsia—hypertension, proteinuria, endothelial dysfunction and placental defects. But to show that these autoantibodies are indeed causally linked to the disease, it was necessary to show that purification and injection of these human autoantibodies into a healthy organism (in this case, a mouse) would cause preeclampsia.

This was exactly what Xia and her colleagues found. Importantly, the team also showed that blocking receptor activation by co-injecting the antagonist losartan or a neutralizing peptide prevented preeclampsia in pregnant mice. Whether this insight will translate to the clinic remains to be seen, but for now this new rodent model of preeclampsia also provides an important research tool.—*RL*

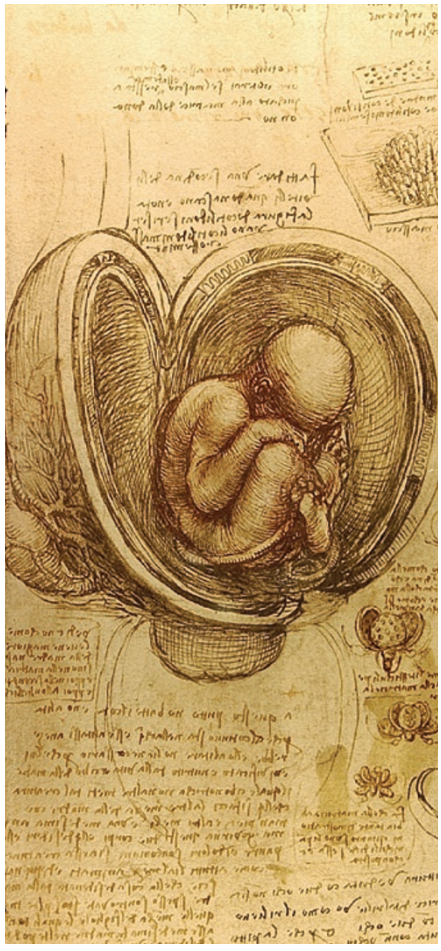


Photo by Luc Viatour GFDL/CC

A fat chance to implant

Successful pregnancies depend on proper embryo implantation, the underlying mechanisms of which remain poorly understood. In 2005, Xiaoqin Ye *et al.* identified the lipid lysophosphatidic acid (LPA) as an important mediator of this crucial process (*Nature* **435**, 104–108; 2005).

LPA acts through four different receptors—LPA_1–LPA_4. Ye *et al.* found that mice lacking LPA_3 had smaller litters, abnormal embryos and enlarged placentas shared by several embryos. Owing to the similarities between this phenotype and what had been reported in mice lacking cyclooxygenase 2 (COX2), the team set out to establish whether there was a relationship between both signaling pathways.

Indeed, the level of COX2 was low in the uterus of LPA_3-deficient mice, leading to reduced amounts of two essential factors for implantation—prostaglandins E_2 and I_2. Moreover, administration of these prostaglandins to LPA_3-knockout mice rescued the implantation defect.

Although these results disclose a role for LPA_3-mediated signaling on implantation, the actual mechanistic link between LPA and COX2 remains to be further investigated.—*JCL*

Written by Eva Chmielnicki, Alison Farrell, Randy Levinson, Juan Carlos López & Clare Thomas

Breath of fresh air

A derivative of estrogen—2-methoxyoestradiol (2-ME)—has a key role in the pathogenesis of preeclampsia, according to research published in *Nature* this year (453, 1117–1121).

A distinctive manifestation of preeclampsia is a small placenta, which may be insufficient for proper oxygenation of the fetus. In fact, another characteristic of the disease is the activation of hypoxia-inducible factor-1α (HIF-1α) in the placental vasculature. Previous work had shown that 2-ME normally increases during pregnancy and that this molecule can inhibit HIF-1α. Keizo Kanasaki *et al.* therefore studied pregnant mice lacking catechol-*O*-methyltransferase (COMT)—the 2-ME–generating enzyme—hypothesizing that the absence of 2-ME would cause preeclampsia.

The COMT-knockout mice indeed showed the typical signs of the disease, which the authors were able to reverse by therapeutically increasing 2-ME levels. Moreover, the authors determined that women with preeclampsia have low concentrations of 2-ME and of placental COMT during the third trimester of pregnancy.

In addition to illuminating a new aspect of the pathophysiology of preeclampsia and raising the possibility of treating the disease by restoring 2-ME levels, the findings also have diagnostic implications: as 2-ME concentrations can be easily detected, they could become a biomarker for this condition.—*JCL*