Reproductive Sciences
18(5) 417

DOI: 10.1177/1933719111406379
http://rs.sagepub.com

In the Spotlight

Maria Rosa Maduro, PhD

How the Skeleton Influences Male Fertility

The gonads have long been known to regulate bone remodeling through the sex steroid hormones, which are essential to maintain bone integrity. A well-known example of this relationship is the onset of bone loss and osteoporosis in postmenopausal women due to a decreased production of estrogen by their ovaries.

On the other hand, a reciprocal effect between the bone and the gonads had never been reported until very recently. Oury et al have just published in the journal *Cell* (*Cell.* 144:796-809) their surprising discovery that osteocalcin, a factor produced by bone cells, induces synthesis of testosterone in the testis, thus acting as a regulator of male fertility.

In their study, Oury and colleagues were able to show that in mice the osteocalcin produced by the bone osteoblasts (the cells responsible for the bone built up during the constant bone remodeling that occurs throughout life) is able to instruct the Leydig cells to produce testosterone, ultimately promoting sperm production. Through tissue-specific inactivation of bone osteocalcin, the authors observed a decrease in testosterone production that led to increased germ cell apoptosis, decreased testis weight and sperm count and, consequently, diminished male fertility. Interestingly, no alterations were observed in female fertility in these osteocalcin-deficient mice.

Oury et al were able to further explore the mechanism by which osteocalcin impacts testosterone biosynthesis. Indeed, the authors identified a testis-specific orphan G-protein-coupled receptor, Gprc6a, as the receptor for osteocalcin in Leydig cells and demonstrated that osteocalcin regulates the expression of enzymes required for testosterone production in a cAMP response element-binding (CREB)-dependent manner.

Since so many forms of male infertility remain idiopathic, these findings by Oury et al certainly suggest that the osteocalcin–Gprc6a pair may provide new etiologies for this condition. Furthermore, besides providing the first evidence for the skeleton as an endocrine regulator of reproduction, this study demonstrates and reinforces the idea that bone plays a much bigger role in whole organism physiology than previously anticipated.

A Helping "Hand" Toward Successful Embryo Implantation

Progesterone is well known to be a key player counteracting the estrogen-mediated uterine epithelium proliferation that occurs during the reproductive cycle in order for successful embryo implantation to occur. The molecular mechanism by which progesterone acts has, however, remained unclear. Li et al have now advanced a step forward toward the unraveling of this mystery.

As recently reported in *Science* (*Science.* 331:912-916), Li and colleagues were able to demonstrate that progesterone induces the expression of a basic helix-loop-helix transcription factor, Hand2, in the uterine stroma that is able to suppress the production of several fibroblast growth factors, which normally act as paracrine mediators of estrogen by promoting its mitogenic effects on the uterine epithelium.

By creating a conditional Hand2 knockout in the adult mice uterine epithelium, Li et al observed that there was a failure to establish pregnancy, despite normal ovarian function, ovulation, and fertilization. These observations lead the authors to conclude that in the absence of Hand2 expression in the stroma, the luminal epithelium fails to acquire competency for embryo implantation. Li and colleagues determined that in Hand2-deficient animals there is a continued induction of fibroblast growth factors in the uterine stroma that, through the ERK1/2-signaling pathway, maintain the estrogen-induced effects and the consequential epithelium proliferation.

In sum, Li and colleagues have elegantly demonstrated that Hand2 is a critical regulator of the uterine stromal epithelium that assures proper steroid regulation necessary for the establishment of pregnancy. Hand2 expression abnormalities may therefore be further investigated in humans as potential causes of unexplained female infertility cases. In addition, since the antiproliferative action of progesterone is of clinical significance in estrogen-dependent endometrial cancer, Hand2 may also be considered a potential target for therapy as a blocking agent of the estrogen proliferative actions.