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## Male Fertility Is in the Bones: First Evidence That Skeleton Plays a Role in Reproduction

***Researchers at Columbia University Medical Center have discovered that the skeleton acts as a regulator of fertility in male mice through a hormone released by bone, known as osteocalcin.***

The research, led by Gerard Karsenty, M.D., Ph.D., chair of the Department of Genetics and Development at Columbia University Medical Center, is slated to appear online on February 17 in *Cell*, ahead of the journal's print edition, scheduled for March 4.

Until now, interactions between bone and the reproductive system have focused only on the influence of gonads on the build-up of bone mass.

"Since communication between two organs in the body is rarely one-way, the fact that the gonads regulate bone really begs the question: Does bone regulate the gonads?" said Dr. Karsenty.

Dr. Karsenty and his team found their first clue to an answer in the reproductive success of their lab mice. Previously, the researchers had observed that males whose skeletons did not secrete a hormone called osteocalcin were poor breeders.

The investigators then did several experiments that show that osteocalcin enhances the production of testosterone, a sex steroid hormone controlling male fertility. As they added osteocalcin to cells that, when in our body produce testosterone, its synthesis increased. Similarly, when they injected osteocalcin into male mice, circulating levels of testosterone also went up.

Conversely, when osteocalcin is not present, testosterone levels drop, which causes a decline in sperm count, the researchers found. When osteocalcin-deficient male mice were bred with normal female mice, the pairs only produced half the number of litters as did pairs with normal males, along with a decrease in the number of pups per litter.

Though the findings have not yet been confirmed in

humans, Dr. Karsenty expects to find similar characteristics in humans, based on other similarities between mouse and human hormones.

If osteocalcin also promotes testosterone production in men, low osteocalcin levels may be the reason why some infertile men have unexplained low levels of testosterone.

**Skeleton Regulates Male Fertility, But Not Female**

Remarkably, although the new findings stemmed from an observation about estrogen and bone mass, the researchers could not find any evidence that the skeleton influences female reproduction.

Estrogen is considered one of the most powerful hormones that control bone; when ovaries stop producing estrogen in women after menopause, bone mass rapidly declines and can lead to osteoporosis.

Sex hormones, namely estrogen in women and testosterone in men, have been known to affect skeletal growth, but until now, studies of the interaction between bone and the reproductive system have focused only on how sex hormones affect the skeleton.

"We do not know why the skeleton regulates male fertility, and not female. However, if you want to propagate the species, it's probably easier to do this by facilitating the reproductive ability of males," said Dr. Karsenty. "This is the only rationale I can think of to explain why osteocalcin regulates reproduction in male and not in female mice."

**Other Novel Functions of Osteocalcin Reported Earlier**

The unexpected connection between the skeleton and male fertility is one of a string of surprising findings in the past

few years regarding the skeleton. In previous papers, Dr. Karsenty has found that osteocalcin helps control insulin secretion, glucose metabolism and body weight.

“What this work shows is that we know so little physiology, that by asking apparently naïve questions, we can make important discoveries,” Dr. Karsenty says. “It also shows that bone exerts an important array of functions all affected during the aging process. As such, these findings suggest that bone is not just a victim of the aging process, but that it may be an active determinant of aging as well.”

#### Next Steps and Potential Drug Development

Next, the researchers plan to determine the signaling pathways used by osteocalcin to enhance testosterone production.

And as for potential drug development, since the researchers have also identified a receptor of osteocalcin, more flexibility in designing a drug that mimics the effect of osteocalcin is expected.

Whether it's for glucose metabolism or fertility, says

Dr. Karsenty, knowing the receptor will make it easier for chemists to develop a compound that will bind to it.

“This study expands the physiological repertoire of osteocalcin, and provides the first evidence that the skeleton is a regulator of reproduction,” said Dr. Karsenty.

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