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REPRODUCTIVE ENDOCRINOLOGY

OSTEOCALCIN AND MALE FERTILITY

Osteocalcin, a hormone secreted by osteoblasts, is important for human male fertility, a new study reveals.

Previous experiments have shown that osteocalcin promotes testosterone biosynthesis in mice testes by interacting with the G-protein-coupled receptor GPRC6A. However, the relationship between osteocalcin and luteinizing hormone, the main regulator of testosterone production in Leydig cells, is unclear. Oury *et al.* have now extended their previous study and show that osteocalcin regulates male fertility in humans and in mice independently of luteinizing hormone.

"We used a combination of cell biology approach and cell-specific gene deletion experiments in mice for the first part of the work; for the second part, we relied on exon sequencing to search for mutations in human patients of interest," explains senior investigator Gerard Karsenty. "These patients were selected because they had a phenotype similar to the one of mice lacking osteocalcin: sterility, low testosterone and high luteinizing hormone levels."

The exons of *BGLAP*, the gene which encodes osteocalcin, and *GPRC6A* were sequenced in 59 male patients diagnosed as having oligospermia. Two patients harboured an identical transversion in a transmembrane domain of *GPRC6A*, which was absent in 942 control individuals with a normal quality and quantity of sperm. Transfection experiments showed that the amino acid substitution in *GPRC6A* prevents the receptor from localizing to the cell membrane. The mutation affected a highly conserved residue and acts as a dominant negative mutation, resulting in loss-of-function of the osteocalcin receptor. However, further experiments are needed to prove that this transversion is sufficient to cause the infertility phenotype.

The authors propose that *GPRC6A* might be a new locus for primary testicular failure in humans, the cause of which is often unidentified. Furthermore, as osteocalcin also regulates insulin secretion, the mutation could also be associated with metabolic defects. The investigators note that both patients with mutations in *GPRC6A* had a history of glucose intolerance as well as disrupted reproductive hormone levels.

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