Stronger case for osteocalcin

By Aaron Bouchie, Senior Writer

In 2007, a paper in *Cell* showed that the hormone osteocalcin could improve glucose homeostasis, thereby suggesting a potential strategy to treat certain metabolic disorders. Questions remained, however, about whether the study's results were influenced by the use of genetically modified animals. Now, a follow-up study published in the *Proceedings of the National Academy of Sciences* by **Columbia University** researchers may lay the issue to rest by showing similar results in wild-type mice.

The results are encouraging for **Escoubac Inc.**, a company launched last year to develop therapies based on the osteocalcin findings. The company focuses on using osteocalcin to treat metabolic disorders such as type 2 diabetes and obesity. Escoubac is the first occupant of **Biogen Idec Inc.**'s Biogen Idec Innovation Incubator in Cambridge, Mass.¹

Gerard Karsenty, lead author on both the *Cell* and *PNAS* papers, told *SciBX* the idea that the skeleton could regulate energy metabolism came about while he was at **Baylor College of Medicine**, where his lab discovered that the hormone leptin was involved in bone remodeling.^{2,3} Most hormones are controlled by feedback loops so that a cell affected by a hormone can send signals back to the cell that produced the hormone. Because leptin is produced in adipose tissue, Karsenty and colleagues reasoned that bone cells may produce hormones that affect fat cells.

The researchers chose to examine osteocalcin because it is one of the few osteoblast-specific proteins that has several features of a hormone: its expression is cell specific; it is synthesized as a preprohormone, which is cleaved twice within the cell before becoming functional; and it is secreted into the general circulation.⁴

In the *Cell* paper, Karsenty's group generated osteocalcin knockout mice, which had higher blood glucose levels, fat mass and triglycerides, and lower serum insulin levels, insulin secretion, insulin sensitivity, glucose tolerance, energy expenditure and β -cell mass and proliferation than in normal mice.

One issue, said Karsenty, was that the results were seen in genetically modified animals. "Some knockout mice can have developmental defects and it is good to have confirmation in wild-type mice," he said.

Thus, in the *PNAS* paper, the researchers used wild-type mice.⁵ Mice implanted with pumps delivering 0.3 or 3 ng/h of osteocalcin had significantly lower blood glucose levels and higher serum insulin

levels and β -cell proliferation than did vehicle controls. Mice in those dose groups also had greater insulin sensitivity than controls, and mice in the 3 ng/h dose group had decreased fat mass.

The researchers also showed that osteocalcin protected wild-type mice against obesity and diabetes compared with vehicle control in two different models of obesity.

The positive effects of osteocalcin on glucose and insulin levels and β -cell proliferation were not seen at a dose of 30 ng/h. However, that dose produced better improvements in fat mass and insulin sensitivity than the lower doses.

Thus, overlapping—but different—amounts of osteocalcin affect insulin secretion and β -cell proliferation on the one hand and insulin sensitivity and fat mass on the other.

A potential explanation for the differential effects is that osteocalcin produces variable effects on gene expression in different cell types. *In vitro*, osteocalcin doubled expression of insulin and β -cell proliferation genes in islet cells at concentrations as low as 0.03 ng/ml and in β -cells at concentrations as low as 0.3 ng/ml. The effects decreased at higher doses.

In contrast, osteocalcin did not significantly increase expression of the insulin sensitivity regulator adiponectin in adipocytes until the dose of the hormone reached 1 ng/ml, and the effects increased at higher doses.

"Now we've shown *in vivo* that osteocalcin works on islets, β -cells and adipocytes, but they have different sensitivities," said Karsenty. "There is some overlap, so whether that area of overlap is a therapeutic dose is another question."

For Escoubac, one of the main challenges will be to find the optimal osteocalcin dosage that will work for different cell types. Karsenty, who also is chairman of Escoubac's scientific advisory board, noted that dosage and toxicology studies required for the company's IND filing are being done at another laboratory.

Nils Bergenhem, CSO of Escoubac, would not disclose when the company plans to file an IND.

Bergenhem did say the *PNAS* paper "will strengthen biological and physiological support of osteocalcin as a drug candidate." He told *SciBX* he was excited by the finding that osteocalcin acts directly on β -cells. "Nothing out there increases the proliferation of β -cells to this degree," he said.

Bergenhem noted that end-stage type 2 diabetics experience β -cell failure and become more like type 1 diabetics. "Osteocalcin could stabilize patients or even improve β -cell function, keeping them in type 2 status and out of end-stage," he said.

Karsenty said his team is trying to identify the osteocalcin receptor on the surface of β -cells. He also said the next step for his lab will be "to see if osteocalcin has the same beneficial effects if it is injected once a day instead of delivered continuously with an implanted pump."

Such tests will determine whether osteocalcin behaves like insulin, which provides the same effects whether given intermittently or continuously, or like parathyroid hormone, which has the opposite effect when given continuously vs. once a day.⁶

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