“That Feeling in Your Bones” with Gérard Karsenty

Transcript of Cerebrum Podcast

Guest: Gérard Karsenty, M.D., Ph.D., is a professor and chair of the Department of Genetics and Development at Columbia University Medical Center. Karsenty, who was trained as an endocrinologist, has used clinical data, evolutionary history, and mouse genetics to study all aspects of skeletal biology. His laboratory identified the master genes of bone formation and parathyroid gland development. His laboratory was also the first to demonstrate the existence of a central control of bone mass, to uncover its road map, and to establish that bone is an endocrine organ. He showed that the bone-derived hormone osteocalcin is necessary, in mice and in humans, for glucose homeostasis, male fertility, and cognitive functions. Karsenty was awarded his Ph.D. and M.D. degrees at the Medical School of the University of Paris V. He is a member of the editorial board of Cell Metabolism, Genes and Development and the Journal of Cell Biology.

Host: Bill Glovin serves as editor of Cerebrum and as executive editor of the Dana Foundation. He was formerly senior editor of Rutgers Magazine, managing editor of New Jersey Success, editor of New Jersey Business magazine, and a staff writer at The Record newspaper in Hackensack, NJ. Glovin has won 20 writing awards from the Society of Professional Journalists of New Jersey and the Council for Advancement and Support of Education. He has a B.A. in Journalism from George Washington University.

Bill Glovin: Do you ever wonder about what makes you feel like danger might be lurking? Are there hormones inside us that make us remember things or reproduce better, or hormones linked to anxiety or depression?

Hi, and welcome to the Cerebrum podcast. I'm Dana Foundation Executive Editor Bill Glovin. And today on the phone with us, to help answer some of those questions, is Gérard Karsenty, the author of our story titled, “The Feeling in Your Bones,” in the recent summer issue of Cerebrum magazine, which you can find at Dana.org.

First, a little about Dr. Karsenty, who is a professor and chair of the Department of Genetics and Development at Columbia University Medical center. He’s one of the world’s foremost experts on a hormone found in the bone called osteocalcin. In 2013, the New Yorker published an article that featured Dr. Karsenty titled, “Do Our Bones Influence Our Minds?”

I love the way you start the article, Gérard, with, “The story begins very far from neuroscience.” Can you tell us what that means?

Gérard Karsenty: Thank you, Bill. Yes, the story starts very far from neuroscience. I was a young assistant professor and I was in search of a project, and I was fascinated by why
is it that mineralization, calcification, appears in bone and in no other tissues. And at that time, there was protein that nobody knew what it was doing, but was suspected to be involved in mineralization, and that was osteocalcin. Those are the early '90s, when making knockout (a genetic technique in which one of an organism's genes is made inoperative) was really heroic.

So, I did the knockout of these genes, and lo and behold, the mice were normal, apparently normal. They have normal, mineralized bones, and bones were normal. And I thought: ‘There it is; that's the end of my career. I will not get tenure with that.’ I had put all my eggs in the same basket, and it did not work. And then, after this first reaction, I came to the conclusion that evolution could not have invented a gene so late during evolution with bone, just for the purpose of inventing a gene. And if this gene has no function in bone, it maybe it has a function in other tissue.

And one reason to think that is that osteocalcin is circulating in the ng/ml range. So, we began to analyze the mice in the hope of finding a phenotype outside bone and the first thing we noticed is that when we kill the mice and opened them up to get to the bone, there were much more fat in these mice than in wild type mice. They were not obese, but they had more fat and then osteocalcin-null mice did not reproduce well.

The third phenotype that we noticed, everybody noticed in the lab, is that these mice were incredibly docile. You could take them in your hands, they will not try to escape, they will not bite. And everybody noticed that. So that shifted the emphasis from this molecule from being mineralization inducer to maybe being a hormone, and that started the work. And the work was based on the hypothesis that there must be a coordinated regulation endocrine in nature of bone growth, energy metabolism and reproduction, and that osteocalcin may be a hormone made by bone that regulates reproduction and energy metabolism. That's how it started.

The way it went to neuroscience is that when we realized the mice were really docile, and abnormally docile, and so we analyzed the phenotype and realized that osteocalcin is needed for spatial memory, is preventing anxiety, and depression. The analysis of these phenotypes was extensive in my laboratory and the one of Eric Kandel. And so, this has really was a rupture in our hypothesis because here, you have a hormone that regulates energy metabolism and reproduction as expected, but memory and anxiety have nothing to do with that.

And we tried to understand why this hormone has its function. What is the commonality between these functions? And one of them, was the one we focused on was, if you look at osteocalcin in term of evolution, memory was not invented to go to medical school. It was invented to remember where there was a predator an hour ago, or the food yesterday.
The ability to metabolize glucose is intimately linked to the ability to flee danger. And that led us to believe that osteocalcin was, in fact, a hormone that is here to prevent or to avoid danger, and that's what led to the testing if it was a stress hormone. It took many years to get there, but that's the logic behind it.

Bill Glovin: Can you describe for our listeners exactly what osteocalcin is? I've heard it described as a protein and a hormone, and maybe a gene. Is it all those things? Is it one of those things?

Gérard Karsenty: This is a hormone, by all criteria. It has a structure of a hormone. It is made from preproprotein protein. It is secreted in blood in the nanograms/ml. It binds to its receptor that we have identified. The receptor, when mutated in a human gives the same disease and in mice. There are all criteria of a hormone are present in osteocalcin. It also has the circadian rate. There is nothing that distinguishes osteocalcin from insulin, for instance. They both fulfill the same criteria of a hormone.

I would add another criterion is that osteocalcin is cell-specific gene, and most peptide hormones, for reasons that are not clear, are cell-specific genes. There is really all the criteria that one, you would expect to describe it as a hormone, including, of course, the receptor, the knockout of the hormone and the phenotypes, the knockout of the receptor in mice and in humans.

I think the most important aspect of the hormone is not the knockout which strikes the mind of most, it is that it fulfills the original definition of a hormone if you inject a hormone into an animal you elicit a response. Mice that have too much osteocalcin have the opposite phenotype of the osteocalcin-null mice.

Bill Glovin: So, if you’re comparing it to insulin in a sense, is there a way to regulate how much osteocalcin we have?

Gérard Karsenty: There is a way to regulate how much osteocalcin we have. We know some of its ways. There are several ways. But there is a way to regulate how much osteocalcin we have. I would say there is two aspects of osteocalcin that are important. Circulating osteocalcin levels go down around 25-year old in woman then go almost to zero; they don't decrease, they disappear. And in man around 40-years-old.

And it suggests that it is a hormone that was here from the time we were supposed to live, during evolution, and it was taking care of functions that are functions of young people, reproduction, memory, running, are the functions regulated by osteocalcin. This now takes another importance, since in our society, these functions are affected by aging and that may be cured potentially by osteocalcin, at least, in the mouse. We are testing if this can be expanded to other species. That's the first aspect that is important.
The second aspect, and again, we don't know what it means, but it is rather unusual for a hormone, is that osteocalcin is a little bit like the godfather. It is a very respectable molecule it does not do much but rather it recruits, it regulates the synthesis of other molecules that actually do its job. It does not regulate reproduction, but it regulates testosterone, which does regulate reproduction. It does not regulate memory, but it regulates monoamine transmitter, BDNF and other neurotransmitter that do the job. It does not regulate glucose metabolism, but it regulates insulin.

This is probably the only hormone I know that is extreme as of so many hormones. It is a little bit as if the invention of bone during evolution, because of the energetic cost that bone growth and bone remodeling entail, has obliged evolution to come up with new ways to regulate old physiological functions, and has put in bone an endocrine center that, in fact, is extreme of many other functions, and we are discovering new functions as we go.

Bill Glovin: It sounds a little bit like osteocalcin is, if you'll forgive me, like the Rodney Dangerfield of genetics or neuroscience, in the way it doesn't really get much respect, or we don't hear about it very much. Is that true? I mean, is this something that is pretty much under the radar in the neuroscience world?

Gérard Karsenty: I think what doesn't get any respect is not osteocalcin, but rather bone. And the reason is not rational, so it is much more formidable obstacle to overcome than scientific one, it is. And I tell you what the reason is. If you are in New York City or in Paris or in Beijing or in Melbourne and you want to represent danger to people in the street, what do you represent? You represent a bone. Bone is a symbol of death, so it's very difficult even for scientists to overcome the idea that the symbol of death could be a source of life. And this is why bone biology as a whole, the way we have redefined it, not bone formation and bone resorption, but endocrinology is suffering because nobody never asks, for instance, when Leptin was discovered, why fat, because fat has no [inaudible 00:12:45]. But for bones, everybody asks me, why bone? And they always add: “I always thought bone was a dead tissue of calcified tubes.”

Bill Glovin: Does exercise help partly because it works to maintain bones, which makes osteocalcin?

Gérard Karsenty: No, exercise won't because it makes osteocalcin, and so it allows an increase in brain function, it decreases anxiety, increases memory and it allows to improve all the functions regulated by osteocalcin, whether it is energy expenditure, or glucose metabolism and obviously body weight.

And so, the effect of exercise on bone mass, is due to a large extent, we think, to the fact that circulating osteocalcin levels increase during exercise.
Bill Glovin: Just to shift gears for a minute. I read that you were born in Algeria and educated in Paris. Tell us about your path to become a geneticist.

Gérard Karsenty: Yeah, so I was born in Algeria which at that time was part of France, and my family had been in Algeria for 500 years, coming from Spain after the Inquisition. And then I moved to France and I went to Medical school and I had a rotation as a medical student in a rheumatology department and I became fascinated with bone disease and bone biology.

And at the end of my fellowship in France, I was sent to the U.S. for post doc that has now lasted 35 years. I became a geneticist and at the end of my post doc, when I became assistant professor, I was asking, what do I want to study? And I thought I want to study bone. I never thought that bone was an endocrine organ, but I wanted to study bone, and that's what I did.

The things that may be a little bit different from some colleagues is that when I realized that osteocalcin null mice had no bone phenotype, but had some peculiar abnormality, instead of dismissing them, I used them to build a whole program, research program. So, in a nutshell, that's my professional life.

Bill Glovin: Is osteocalcin being studied by other geneticists or neuroscientists? It's interesting in the sense that it's kind of the merging of two, almost completely different fields. It is a great example of how science works cross-functionally.”

Gérard Karsenty: About 25 to 30 labs in the world that are working on osteocalcin in mice and in humans. Some of them, like us, are doing neuroscience. Many of them are doing energy metabolism. Neuroscience is part of our project as you see with this article, but we are also delving into new areas of research that are all centered around the notion that the bone may have been invented by evolution, in part, as a survival tool when animals left the sea to go to land.

And what we are trying to write now is a new chapter of the physiology of danger through osteocalcin. But the function of bones, the classical function of bones, fits this definition because while you are sitting and listening to me, if the ceiling falls on your head, you will be unhappy, but you will not die, because bone protects your brain.

To hear, you need bones that are in your middle ear. And if you cannot hear, there is no way you can survive in the wild, and without bone, you cannot run, of course. So the most elementary function of bone are also needed to escape danger, and therefore bone via its classical and endocrine functions is nothing less than an organ designed to fight danger.

Bill Glovin: So one of the interesting parts of your article, I thought, when you’re talking about osteocalcin and a sense of danger, was that how most people feel adrenaline is the thing that makes you react, but osteocalcin plays just an
important a role, if not more of a role in that aspect. Am I correct in assuming that?

Gérard Karsenty: Well, osteocalcin plays more of a role than adrenaline because as you have seen in the paper, if you look at mice or human that have no adrenal glands, so they don't have cortisol of adrenaline, yet if you stress them, they have a normal stress response. But if you take animal that have no osteocalcin, or no osteocalcin receptor, they cannot have stress response in front of stressors.

And what we have shown is that the reason why adrenalectomized animal and humans have normal stress response is because they have too much osteocalcin. response. So, yes, so stress response is determined by bone and osteocalcin, not by the adrenal gland and adrenaline.

Bill Glovin: So, what is the next frontier for osteocalcin research? What are you trying to achieve going forward?

Gérard Karsenty: What I'm trying to achieve going forward are multiple things. The first one is to strengthen the notion that osteocalcin is a hormone of danger by looking at other functions, which we are doing, and by looking in the brain and other aspects of neuroscience.

The second thing that we are trying to achieve is to demonstrate that osteocalcin is a treatment of several manifestation of aging such as age-related memory loss, the decline in the ability to exercise, to decline in the handle glucose and the decline in fertility in men.

And so, we want to turn the table around about osteocalcin and take advantage of its biology, which occurs only in young humans, to see if we can introduce now in old humans and rejuvenate some of the functions. So those are both very fundamental, but almost conceptual goals to demonstrate that osteocalcin is a master hormone of danger and some almost clinical goal to demonstrate the clinical relevance of osteocalcin.

Bill Glovin: So, getting back to where we began with that New Yorker article, do our bones influence our minds, I think at this point, there's no question that it does.

Gérard Karsenty: There is no question, absolutely. There are always naysayers who said I prefer the world as it was 50 years ago, and I prefer bone as it was before it became an endocrine organ. But no, the evidence is overwhelming, and they're overwhelming because they come from so many labs, in so many countries. So, there is no way to stop data right now.

Bill Glovin: I think that's a great place to end. I can't thank you enough. And I just would like to remind listeners that you can read more about this in greater detail in Dr. Karsenty's story in the summer issue of Cerebrum called, “That Feeling In Your Bones,” at Dana.org. Thanks for listening and stay healthy and safe in this
difficult pandemic that we are experiencing now. So, thank you, doctor. It was indeed an honor and a privilege to have you write for us.

Gérard Karsenty: Thank you very much, Bill.