QnAs with Sean J. Morrison

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Sean Morrison has spent his career studying the mechanisms that regulate stem cell function and the ways in which these mechanisms influence cancer development. He has discovered several important regulators of stem cell self-renewal, as well as factors that influence the self-replication of cancer cells. In addition, Morrison has identified the location and cellular composition of the microenvironment of hematopoietic stem cells in adult bone marrow and spleen. Morrison's work on hematopoietic stem cells led to the discovery of a bone-forming growth factor that he named osteolectin (1). In his Inaugural Article, Morrison describes recent work on the mechanisms by which osteolectin influences bone formation (2). Morrison is now an HHMI Investigator at the University of Texas Southwestern Medical Center and was elected to the National Academy of Sciences in 2020.

Sean J. Morrison. Image credit: Children's Medical Center Research Institute at UT Southwestern.

PNAS: How did you become interested in studying bone formation and osteolectin?

Morrison: My laboratory has a longstanding interest in identifying and understanding the niche for hematopoietic stem cells in the bone marrow. About 10 years ago, we discovered a cell type in the bone marrow, leptin receptor-positive stromal cells, that are the key source of growth factors for the maintenance of hematopoietic stem cells. Those cells also include the skeletal stem cells that are the main source of bone and fat cells that form in adult bone marrow. So, we were interested in whether those cells make any novel growth factors. We looked at the factors that are secreted by the leptin receptor-positive cells and we discovered this bone forming growth factor that we named osteolectin (1).

People had known that this protein existed and had assumed it was a hematopoietic growth factor because it was made in the bone marrow, but no one had ever studied its function in vivo. So, we studied osteolectin's function in vivo. We made a lot of knockout mice and reporter mice, which takes time and is a lot more challenging than doing experiments with cell lines in culture. But the value of putting in that extra time to study these mechanisms in vivo is that we were able to study the physiological mechanisms. We knocked out osteolectin from mice and found that it wasn't required for hematopoiesis but it was required to maintain the adult skeleton. It acts on the lectin receptor-positive cells and promotes their differentiation into bone cells. In the absence of osteolectin, you can't make enough bone to maintain the adult skeleton and you develop what looks like early-onset osteoporosis. That revealed a new mechanism for maintaining the adult skeleton, and for the past 5 years we've been interested in understanding more about how osteolectin acts and its physiological function.

PNAS: What did you discover in your Inaugural Article (2)?

Morrison: Parathyroid hormone is a bone-forming agent that's used in people with osteoporosis. Physicians give it to people with osteoporosis, and it increases their bone mass and reduces the risk of fracture. The key advance in the Inaugural Article (2) is the discovery that a substantial part of the mechanism by which parathyroid hormone promotes the formation of new bone is by increasing the expression of osteolectin. So, osteolectin mediates the effect of parathyroid hormone on bone formation. In contrast to parathyroid hormone, sclerostin inhibitor doesn't appear to induce osteolectin expression and osteolectin is not required for bone formation in response to sclerostin inhibitor. So, there are different bone-forming pathways.

This is a QnAs with a member of the National Academy of Sciences to accompany the member's Inaugural Article, e2026176118, in vol. 118, issue 25.

Published June 21, 2021.

PNAS: What are some of the implications of these results?

Morrison: Nobody knew that osteolectin even existed as a bone-forming agent just a few years ago. For years and years, all we had in terms of anabolic bone-forming agents for people with osteoporosis was parathyroid hormone. People respond to parathyroid hormone for a limited amount of time and, once they stop responding, there was nothing else to offer in terms of anabolic agents. What's new is that there are multiple anabolic agents that are becoming available. The [Food and Drug Administration] has already approved parathyroid hormone and sclerostin inhibitor, and now our discovery of osteolectin adds another anabolic agent that could potentially be added to the mix.

The other thing that we found in our paper (2) is that osteolectin, when combined with parathyroid hormone, has additive effects on bone formation. So, we can start to think about improving the treatment of patients either by combining together multiple bone-forming agents or by using them in series, in the same way as we treat people with cancer. For cancer, we've got a first-line agent, and then when that stops working, we've got a second-line agent, and when that stops working, we've got a third-line agent, and there's now the possibility of doing this with anabolic agents for osteoporosis as well. In addition to these practical implications, this paper also adds to our understanding of the mechanisms that regulate the adult skeleton. The Inaugural Article reveals a difference downstream of sclerostin inhibitor and parathyroid hormone in terms of how they promote bone formation.

PNAS: What follow-up experiments are you planning?

Morrison: We're doing a lot of experiments to more fully understand the physiological function of osteolectin. For example, is it required throughout adulthood to maintain the skeleton or is it maybe only required in young adults? Also, does osteolectin expression increase in response to fracture? We are trying to further refine the mechanisms by which it acts and trying to optimize its potency for promoting bone formation. There is probably a lot of heterogeneity among bone-forming progenitors during adulthood, and one of the big questions for the field is which progenitor populations are relevant for what aspects of bone formation and which cells are responding to which factors. We really don't have a good understanding of that, and my expectation is that there's a lot of biology there to study.

1 R. Yue, B. Shen, S. J. Morrison, Clec11a/osteolectin is an osteogenic growth factor that promotes the maintenance of the adult skeleton. *eLife* **5**, e18782 (2016).
2 J. Zhang *et al*, The effect of parathyroid hormone on osteogenesis is mediated partly by osteolectin. *Proc. Natl. Acad. Sci. U.S.A.*, 10.1073/pnas.2026176118 (2021).