The Role of the Osteocyte in Bone and Nonbone Disease

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KEYWORDS

• Osteocyte • Bone disease • Sclerostin • FGF23 • Therapeutics

KEY POINTS

- Within the last decade, the number of studies of osteocytes has increased dramatically leading to the discovery of novel functions of these cells.
- These cells can also be responsible for not only bone diseases and disorders, but also those of the kidney, heart, and potentially muscle.
- Osteocytes have entered the realm of therapeutic targets for bone disease and now potentially kidney disease.
- It will be important not to overlook these cells with regard to the health of other systems and organs.

INTRODUCTION

Before osteocytes were recognized as active essential bone cells necessary for bone health, it was assumed that all the action took place on the bone surface and not within the bone. Osteoblasts and osteoclasts were the major players, osteoblasts making bone and osteoclasts resorbing bone to maintain bone homeostasis. It was assumed that osteoblasts and osteoclasts were regulated by external factors such as parathyroid hormone (PTH) or 1,25 dihydroxyvitamin D_3, and other external regulatory factors. It has also been proposed that osteoblasts make factors that regulate osteoclast activity and, conversely, that osteoclasts make factors that could regulate osteoblast activity. Therapeutics were generated that would target either osteoclasts or osteoblasts. Osteocytes were left out of the picture.

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With new technology and new tools, it became possible to study osteocytes. The normal functions of osteocytes expanded rapidly to include regulation of osteoblast and osteoclast activity to control bone remodeling, as regulators of both phosphate and calcium homeostasis, as mechanosensory cells that coordinate the skeleton's response to loading or unloading, and as endocrine cells targeting other tissues such as kidney. These cells are also one of the longest lived cell types in the body, with some living for decades; therefore, survival and normal function is paramount (**Box 1**). A number of pathologic or disease conditions can now be ascribed to abnormal or missing osteocyte functions, including sclerosteosis, hypophosphatemic rickets, osteoporosis, necrotic bone, and aging (**Fig. 1**). Now therapeutics are being generated that target osteocyte factors (for reviews see[1,2]).

NORMAL OSTEOCYTE FUNCTIONS

Mechanosensation

When early histomorphomists peered through their microscopes and began to visualize osteocytes in bone, the morphology and connectedness suggested a network perhaps similar to the neural system. One of the earliest functions ascribed to osteocytes was mechanosensation based on Julius Wolff's descriptions of the capacity of bone to adapt to mechanical loading or lack of loading by adding or removing bone.[3]

Box 1
Normal functions of osteocytes

- Control mineralization through *Phex*,[123] *Dmp1*,[56] and *MEPE*.[124,125]
- Regulate phosphate homeostasis through *FGF23*.[56,84]
- Play a role in calcium homeostasis in response to parathyroid hormone/parathyroid hormone-related protein.[40,126]
- Can recruit osteoclasts through expression of *RANKL* with or without cell death.[24,113,114]
- Can regulate osteoblast activity through *Sclerostin*.[127,128]
- Are mechanosensory cells through β-catenin signaling.[14,129]
- Have autocrine/paracrine effects through *prostaglandin* production.[6,130,131]
- Under calcium restriction, osteocytes remove calcium from bone through the vitamin D receptor.[132]
- Osteocytes regulate myelopoiesis/hematopoiesis through *G-CSF*.[63]
- *G-CSF* targets osteocytes that mediate mobilization of hematopoietic stem/progenitor cells and is prevented by surgical sympathectomy.[64]
- Osteocytes regulate primary lymphoid organs and fat metabolism[65]
- Osteocytes can dedifferentiate to become a source of matrix-producing osteoblasts.[133]
- Can increase muscle myogenesis and muscle function[60,62,134] and can inhibit muscle mass with aging.[107]
- Can have effects on heart[120,135] and liver[136] through fibroblast growth factor 23.
- Play a role in fracture healing through insulinlike growth factor-1.[137,138]
- Regulate bone formation through Bmpr1a signaling,[139] Notch activation,[140] and ERα signaling.[141,142]
- Suppress breast cancer growth and bone metastasis.[143]

Data from Ref.[1,2,122]