Published in final edited form as:
J Musculoskelet Neuronal Interact. 2006 ; 6(4): 331–333.

Osteocytes as multifunctional cells

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Keywords

Osteocytes; Mechanical Load; Mineral Metabolism

Bone is often thought of as being a passive, inactive tissue like a skeleton hanging in the anatomy lab. Often, bone tissue is envisioned statically in terms of two dimensions similar to a ‘shapshot’ of a histology slide. However, quite to the contrary, bone undergoes considerable turnover as compared to other organs in the body. Modeling during growth is dramatic and even in adult bone, 2–5% turnover per year occurs in the long bone and 30% in alveolar bone. Any experimental approach can bias or have an effect on human interpretations of biological processes and events. Scientists should always be constantly asking how our perceptions are being modified by our experimental approaches.

Bone biologists can easily visualize *in vitro* and *in vivo* the dynamic nature of osteoclasts with their resorption lacunae and rapid removal of bone, which occurs relatively rapidly in days. Osteoblasts are less dynamic, with new bone formation occurring in weeks. Many individuals still view the osteocyte as being a passive, inactive cell that merely acts as a ‘place holder’ in bone. Again, this perspective has most likely been perpetuated by histological approaches to the study of bone. Decades ago there were pioneers in the bone field who proposed that the osteocyte is not a passive cell, but a cell with the potential to have several functions. Credit is given to several of these pioneers below, while contrasting with most recent advances due to the availability of state of the art technology.

Osteocyte conversion of mechanical strain into biochemical signals

Osteocytes, with their distribution throughout the bone matrix and their high degree of interconnectivity, are ideally positioned within the bone matrix to sense mechanical strain and translate that strain into biochemical signals of resorption or formation related to the intensity and distribution of the strain signals[1]. Rubin and Lanyon in 1984 and 1985 developed and characterized the mechanical strain parameters for inducing bone formation or bone resorption *in vivo*[2,3]. However, the major challenge has been and still is to translate *in vivo* parameters of mechanical loading to *in vitro* cell culture models. With the advent of microCT, finite element analysis can be performed. Combined with means to follow gene and protein expression over time, it is now possible to correlate magnitude of strain with biochemical signals and with the final biological response[4,5].

Osteocyte modification of their microenvironment

Over five decades ago, Heller-Steinberg proposed that osteocytes may resorb their lacunar wall under certain conditions[6]. The term “osteolytic osteolysis” was initially used by Belanger in

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The author has patents on MLO-Y4 and A5 cells.

1969 to describe the enlarged lacunae in patients with hyperparathyroidism[7]. This term has been confused with the resorption mechanisms used by osteoclasts as evidenced by investigators placing osteocytes onto dentin slices[8]. The term “osteocyte halos” was used by Heuck[9] to describe pericanicular demineralization in rickets and later by others to describe periosteocytic lesions in X-linked hypophosphatemic rickets[10]. In 1971, it was suggested by Baylink and Wergedahl that the osteocyte has both matrix forming and matrix destroying activities and that the osteocyte can remodel its local environment including lacunae and canaliculi[11]. Osteocyte lacunae were shown to uptake tetracycline, called “periosteocytic perilacunar tetracycline labeling” and were also found to be acid phosphatase positive near endosteal osteoclastic resorbing surfaces. These early observations mainly using histological approaches to suggest that the osteocyte can both add and remove mineral from its lacunae and canaliculi. Using state of the art technology, such as Surface Plasmon and Raman imaging, Lane and colleagues found that mice receiving prednisolone showed an enlargement of osteocyte lacunae in trabecular bone and the generation of a surrounding sphere of hypomineralized bone[12]. The capacity to deposit or remove mineral from lacunae and canaliculi in response to environmental stimuli also has important implications with regards to changes in magnitude of fluid shear stress and mechanical properties of bone.

Osteocytes as regulators of mineralization and phosphate and calcium homeostasis

Pioneers in the isolation and characterization of osteocytes include Peter Nijweide for the isolation of avian osteocytes[13] and Yuko Mikuni-Takagaki for the isolation of murine osteocytes[14,15]. Nijweide identified Pex as being highly expressed in avian osteocytes and Mikuni-Takagaki described osteocytes as being low expressors of alkaline phosphatase, but high expressors of casein-kinase and osteo-calcin. Several osteocyte specific markers such as sclerostin, an inhibitor of mineralization and Dentin Matrix Protein 1, Dmp1, a regulator of mineralization have been identified in osteocytes[16,17]. The fact that these molecules that clearly have a function in mineralization are highly expressed in osteocytes implies that osteocytes can regulate mineralization.

Once the osteoblast begins to transform into an osteoid osteocyte, molecules such as Dmp1, Phex, Mepe/OF45, and sclerostin increase in expression. Recently it has been found that Dmp1 null mice have a similar phenotype to hyp mice in which Phex is mutated and both models are osteomalacic with elevated FGF23 levels. FGF23 has also been found to be highly expressed in osteocytes[18]. Taken together, these molecules, Dmp1, Phex, and Mepe/OF45, would control phosphate metabolism through regulation of this phosphaturic factor, FGF23. The osteocyte lacunocanalicular system could be viewed as an endocrine organ.

Osteocytes can move

Evidence is accumulating that osteocytes are more active than previously known. Dallas and colleagues will show at this meeting that osteocyte cell body movement occurs within lacunae and that extension and retraction of dendrites can occur within canaliculi. These observations were made possible by the recent generation of transgenic mice with green fluorescent protein (GFP) expression targeted to osteocytes[19] and with time-lapse dynamic imaging. Calvaria from these mice were used to image living osteocytes within their lacunae[20]. These studies have revealed that, far from being a static cell, the osteocyte is highly dynamic. Fluid flow through the lacunocanaliculi network would be variable depending on cell body and dendrite movement.

In summary, the proposed functions of osteocytes include the translation of mechanical strain into signals of bone formation or of bone resorption, as modifiers of their microenvironment

thereby modifying the properties of bone and the magnitude of shear stress in the bone fluid, as regulators of mineralization and as regulators of phosphate homeostasis. These cells may act as more than orchestrators of resorption or formation in response to strain. This information and the fact that these cells can move within their lacunae should dispel any notion that these cells are inactive, place holders.

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