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Review

Morphological aspects of the biological function of the osteocytic lacunar canalicular system and of osteocyte-derived factors

Muneteru Sasaki[a], Hiromi Hongo[a], Tomoka Hasegawa[a], Reiko Suzuki[a], Liu Zhusheng[a], Paulo Henrique Luiz de Freitas[b], Tamaki Yamada[c], Kimimitsu Oda[d], Tsuneyuki Yamamoto[a], Minqi Li[a,e], Yasunori Totsuka[c], Norio Amizuka[a,*]

[a] Department of Developmental Biology of Hard Tissue, Graduate School of Dental Medicine, Hokkaido University, Sapporo, Japan
[b] Department of Oral and Maxillofacial Surgery, Dr. Mário Gatti Municipal Hospital, Campinas, Brazil
[c] Department of Oral and Maxillofacial Surgery, Graduate School of Dental Medicine, Hokkaido University, Sapporo, Japan
[d] Division of Biochemistry, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan
[e] Shandong Provincial Key Laboratory of Oral Biomedicine, The School of Stomatology, Shandong University, Jinan, China

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ABSTRACT

Osteocytes are organized in functional syncytia collectively referred to as the osteocytic lacunar–canalicular system (OLCS). The osteocytes are interconnected through gap junctions between their cytoplasmic processes, which pass through narrow passageways referred to as osteocytic canaliculi. There are two possible ways molecules can be transported throughout the OLCS: via the cytoplasmic processes and their gap junctions, and via the pericellular space in the osteocytic canaliculi. Transport of minerals and small molecules through a spatially well-organized OLCS is vital for bone mineral homeostasis, mechanosensing, and bone remodeling control. Recently, osteocyte-derived molecules – sclerostin, dentin matrix protein-1, fibroblast growth factor 23 (FGF23) – have been put in evidence as they may be related to osteocytic functions such as mechanosensing, regulation of bone remodeling, and so forth. FGF23 regulates serum phosphate concentration by affecting renal function, while sclerostin can inhibit osteoblastic activities. In our observations, FGF23 and sclerostin synthesis seemed to be associated with the spatial regularity of the OLCS. This review will introduce our recent morphological studies on the regularity of OLCS and the synthesis of osteocyte-derived FGF23 and sclerostin.

Contents

1. Introduction

Osteocytes, the most abundant cells in bone, are at the center of bone turnover control as they establish the network through which osteoblasts and bone lining cells communicate. All osteocytes lie within osteocytic lacunae and connect to other osteocytes and to osteoblasts on the bone surface. Osteocytes are embedded in the bone matrix, and are derived from osteoblasts that got

* Corresponding author at: Department of Developmental Biology of Hard Tissue, Graduate School of Dental Medicine, Hokkaido University, Kita 13, Nishi 7, Kita-ku, Sapporo, 060-8586, Japan. Tel.: +81 11 706 4223; fax: +81 11 706 4226.
E-mail address: amizuka@den.hokudai.ac.jp (N. Amizuka).

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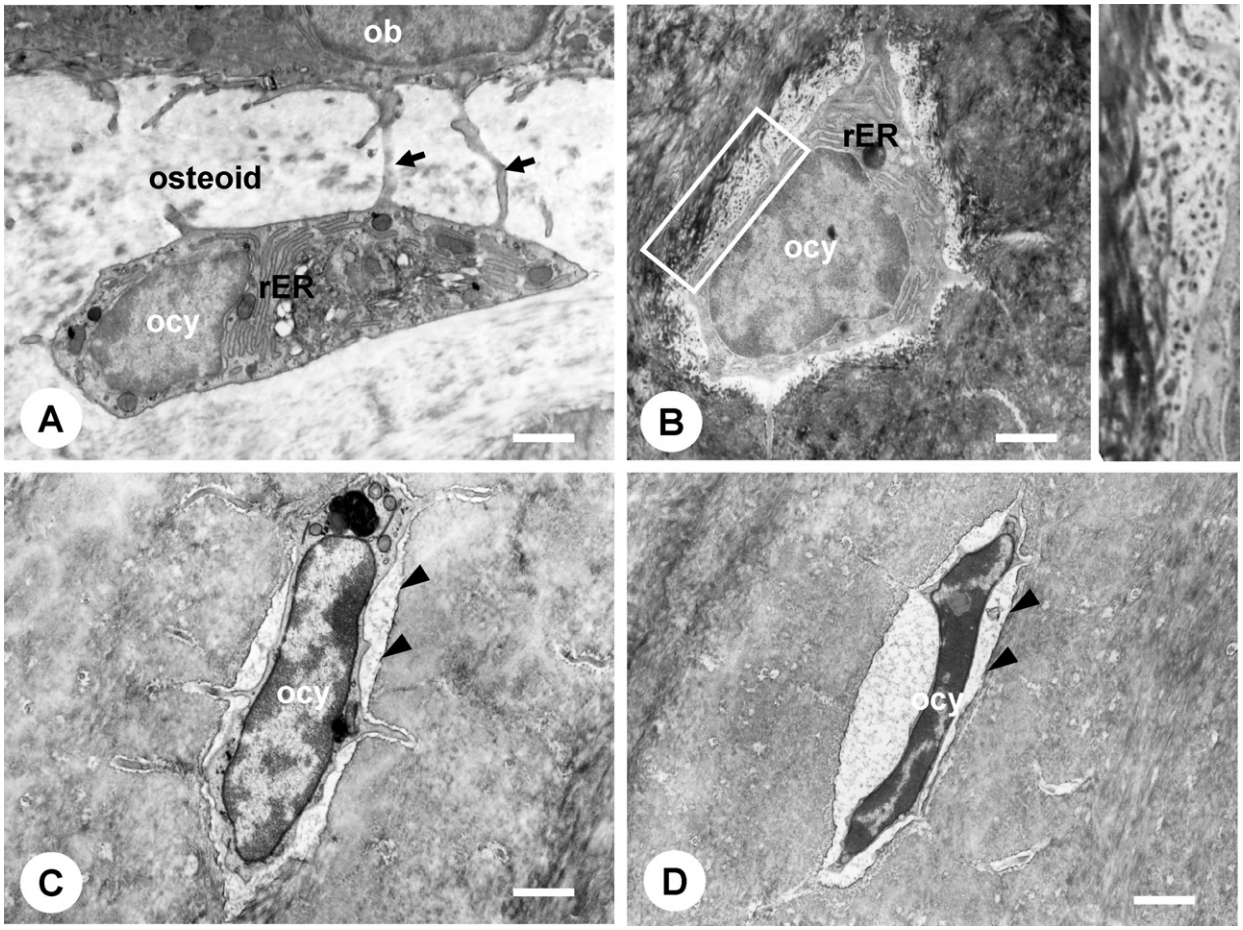

Fig. 1. The ultrastructure of osteocytes depending on the site and on the interval since embedding into the bone matrix. Panel A shows a recently embedded osteocyte (ocy) connected to an osteoblast (ob) by its cytoplasmic processes (arrows). This osteocyte has abundant rough endoplasmic reticulum (rER) and shares ultrastructural similarities with osteoblasts. In panel B, osteocytes close to the bone surface but embedded into mineralized matrix tend to have rER and are surrounded by the rough walls of the osteocytic lacuna. As shown in the right-hand panel, there are collagen fibrils in the pericellular space in the osteocytic lacuna. In contrast, as shown in panels C and D, osteocytes embedded in the deeper portions of the matrix or those that have been buried for a long time show fewer cell organelles, and the nucleus becomes more significant. Please note the nucleus of osteocyte in D was much more condensed than that seen in C. The electron dense lines on the wall of lacunae, the lamina limitans (arrowheads in C and D), indicate the absence of bone deposition. Bar: A–D, 1 μm.

"trapped" within the bone matrix. Depending on the site and on the interval since the embedding, osteocytic ultrastructure can vary significantly (Fig. 1). Recently embedded osteocytes have abundant rough endoplasmic reticulum (rER) and Golgi apparatus, indicating some residual bone formation capacity. Osteocytes close to the bone surfaces have rER, and their osteocytic lacunae have rough walls, suggesting that osteocytes embedded in the superficial bone layers may still be capable of synthesizing bone matrix. Aarden et al. termed osteocytes located in osteoid and those embedded in recently mineralized matrix as osteoid osteocytes and young osteocytes, respectively [1]. In contrast, osteocytes embedded in the deeper portion of matrix or those that have been buried for a long time (mature osteocytes) show fewer cell organelles with the nucleus becoming more prominent.

The process of osteocyte embedding in bone is not at all random. Osteocytes act as a functional group, since their cytoplasmic processes are connected through gap junctions [2–4]. Such a network of cytoplasmic processes permits the passage of small cytoplasmic molecules from one osteocyte to the next. In addition, the pericellular space (annular space) in the osteocytic canaliculi may serve as an alternative transport path (Fig. 2). The diffusion coefficient of fluorescein in the pericellular space has been shown to be similar to diffusion coefficients measured for comparably sized molecules in cartilage matrix [5]. Through these possible paths, embedded osteocytes communicate and establish the osteocytic lacunar–canalicular system (OLCS) [1,6,7]. The three-dimensional OLCS has been examined in vivo [8], and our group has recently demonstrated that, in mice, the OLCS becomes progressively more regular as the individual grows [9].

For the OLCS to function properly, its anatomic arrangement has to be correct. In mature, cortical bone, osteocytic bodies parallel the bone surface and extend their cytoplasmic processes perpendicularly to it (Fig. 3) [10]. This regularity may relate with the direction of the collagen bundles: while the longitudinal axis of the osteocytes parallels the direction of the collagen fibrils, their cytoplasmic processes are perpendicular to them. The regular OLCS may enable the osteocytes to sense mechanical loading and efficiently transport small molecules via their cytoplasmic processes and through the pericellular space of their canaliculi. Bone disease, on the other hand, may significantly affect the arrangement of the OLCS. In human osteomalacia, haphazardly connected, non-regular OLCS are seen, and in the late stage of osteoporosis, a remarkable compromise of connectivity and regularity of that system is present [7].

In this review, we will introduce and elaborate on morphological aspects of osteocytic function, especially the biological function of the regularly arranged OLCS and the pivotal roles of osteocyte-derived factors in bone mineralization.