

# Advances in knowledge about induced tooth movement

## Part 1: The osteocytes

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Osteoblasts and clasts were primary targets for the understanding of bone biopathology. In recent years, evidence has shifted attention to the osteocytes. The biology of induced tooth movement and jaw orthopedics should research the role of osteocytes and the specific effects of mediators such as RANKL and sclerostin. The sclerostin represents a regulatory molecule: When more bone is necessary, osteocytes release less sclerostin, when it is necessary to inhibit bone formation, osteocytes release more sclerostin. RANKL is connected to local osteoclastogenesis in order to have more cells capable of reabsorbing the mineralized matrix. New therapeutic ways of controlling the metabolic bone diseases have been targeted at these mediators.

**Keywords:** Osteocytes. Mechanotransduction. Tooth movement. Sclerostin. RANKL.

The osteocytes have always been placed in a second role in the study of the phenomena associated with tooth movement, as well as in bone biology and comprehension of the diseases involving our skeleton. It was believed that osteocytes were included in the mineralized bone matrix and, thus, did not participate in bone metabolism, the responses to stimuli and aggression.

The dendritic shape of the osteocyte puts it in contact with 40 to 50 cells simultaneously, generating among them a very efficient communicating network, while scavenging any deformation that the bone may suffer from deflections resulting from compression and traction. This osteocytes communicating network acts as excellent

mechanotransducers and also are centrally involved in bone metabolism by releasing mediators that reaches bone surfaces.

As shown in numerous studies over the past five years, there is strong influence of osteocytes in bone remodeling and, by extension and consequence, osteocytes must actively participate in the biopathology of the induced tooth movement, among which is the biology of orthodontic movement.

### **THE ORIGIN OF OSTEOCYTES: PRIMARILY MESENCHYMAL CELLS AND, SECONDARILY, DERIVED FROM OSTEOBLASTS!**

The osteocytes and osteoblasts are mesenchymal cells which differentiate upon stimulation of

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mediators still in the embryo and fetus. The main mediator of differentiation and synthesizing activity in this intrauterine phase are the BMPs or osteomorphogenetics proteins. Mediators in the early stage, that determines the form of organs and structures, can be identified as morphogens, such as it is in these osteomorphogenetics proteins. In this osseodifferentiation and synthesis environment, much of the molecules of these mediators are eventually included in the bone extracellular matrix to be mineralized later. Thus, it can be assured that any mineralized bone matrix has, naturally, osteomorphogenetic proteins in its composition.

Once the skeleton is formed and adulthood is established, osteoblasts and osteocytes remain in bone environment. Many osteoprogenitor cells, pre-osteoblasts and tissue stem cells, formerly known as undifferentiated mesenchymal cells remain on bone surfaces. In the bone marrow, contained and protected by trabeculae and cortical, there are many tissue stem cells, which can originate almost infinitely new bone cells.

Osteoblasts on the surfaces of the trabecular and cortical bone, are polyhedral cells arranged side by side, like a real fence, railing, or palisade. Its polyhedral format allows, on one of its surfaces, bone matrix production, and, in the other surface, expose receptors to mediators located on adjacent connective tissue or bone marrow tissue. At the same time, laterally, osteoblasts contact and interact with other osteoblasts to form a true cell layer covering bone surfaces.

In certain conditions the osteoblasts synthesize the bone matrix and mineralize it; in other conditions, as in inflamed and stressed areas, the mediators can induce osteoblasts and move the bone surface, remain on the periphery and command the clasts activity in the context of an osteo-remodeling unit or BMU.

In this bone matrix deposition many osteoblasts eventually end up included in gaps called osteoplasts (Figs 1, 2 and 3). It was believed for many years that these cells would be trapped, almost by a passive mechanism, as if they had lost the moment to depart, and got involved in the newly deposited matrix. The passive role of osteocytes was proved untrue. On the contrary, these cells seem to perform a central role in controlling bone remodeling and opposite reactions to certain stimuli.

## **THE LOCATION AND SHAPE OF OSTEOCYTES**

Osteocytes comprise 90-95% of bone cells in an adult.<sup>15</sup> These cells are included in the mineralized bone matrix (Figs 1, 2 and 3) and now, as with osteoblasts and clasts, we also have greater knowledge about the osteocytes and their functions.

Osteocytes are regularly distributed in the gaps in the bone matrix, also known as osteoplasts, and communicate with each other and with the cells of the bone surface by means of extensions of the canaliculi of 100 to 300nm thickness.<sup>3,4,5</sup> They form a true web with their extensions, one real network comparable to the neural network in the central nervous system (Figs 1, 2 and 3).

Within these tubules, where the cytoplasmic processes of each cell are (Figs 1, 2 and 3), circulates a fluid tissue that carries nutrients and mediators. These canaliculi with its working fluid and its extensions communicate the osteocytes with each other and interconnected with the surface cells of cortical and trabecular bone, in addition to resident cells of the bone marrow.<sup>10</sup> This communication can be cell-cell by means of specialized junctions or mediators (Figs 1, 2 and 3).

## **THE BONE MECHANOTRANSDUCTORS: OSTEOCYTES**

The osteocytes network form a very sensitive 3D system that uptakes bone deformities. Any change in bone form during skeleton function can be captured by this sensitive network or web of osteocytes, and extensions or mechanotransduction detection system. Exercise can increase bone structure by mechanical stimuli, initially, on this network scavenging strain.

The osteocytes individually pick up signals by mechanical deformation of their cytoskeleton. At the same time, the network in which each osteocyte participates, distributed throughout the bone structure, picks up deformations, overloads, deflections and limitations of nutrients. The deformation of the cytoskeleton, the restriction of oxygen and of nutrient stress the osteocytes, which release mediators to communicate with other osteoblasts and clasts on the bone surface and induce them to reactive or adaptive phenomena.

When we deform, compress or strain the bone as happens during orthodontic movement, we put the

osteocytes in mechanical stress and, thus, it increases the production of secreted and circulating mediators through the fluid that circulates in the canaliculi (Figs 1, 2 and 3) and from there to the respective periodontal and bone surfaces. Although included in the mineralized bone matrix in their osteoplasts, the osteocytes and its communicating network – by direct contact or mediators – can stimulate or inhibit bone formation and bone resorption in the “distant” cortical bone surface (Fig 3). The osteocytes in the bone marrow inside the bone, can influence the higher or lower production of clastic cells and osteoclastogenesis.

The osteocytes, therefore, have a strong influence in the function of bone to adapt its shape according to the determination of functional demands, changing the mechanical stimuli into biochemical events, a phenomenon known as osteocyte mechanotransduction.<sup>13</sup> The osteocytes also play a role in regulating the mineral metabolism<sup>9</sup> and also induce changes in the properties of bone matrix around it,<sup>12</sup> but these functions were already better known.

The skeleton is able to continuously adapt to mechanical loads by the addition of new bone to increase the ability to resist or remove bone in response to a lighter load or lack of use.<sup>6,8</sup> The osteocytes have a high interconnectivity and are considered the bone mechanotransducers.



**Figure 1** - The osteocyte network participates of the cellular functional control on bone surface, such as the clasts and osteoblasts. The cytoplasmatic prolongations arrive at the canaliculi and make contact with the surface cells or act via mediators (HE; 40X).

Osteocytes increases glucose-6-dehydrogenase phosphatase after a few minutes of load,<sup>18</sup> a marker for increased metabolism, as it occurs in cells associated with bone surface. Seconds after the applied load on the osteocytes, nitric oxide prostaglandins and other molecules such as ATP<sup>1</sup> are increased.

Therefore, osteocytes, when facing induced loads, have the ability to release mediators, which stimulate the precursors of clasts or osteoclastogenesis to differentiate into new clasts increasing the rate of resorption. Among these mediators the M-CSF or stimulating factor of colonies for macrophages and RANKL should be highlighted.<sup>14</sup> It can be argued that osteocytes can command the activities of the clasts on bone surfaces according to functional demand. The set or lacunocanicular osteocyte system can be seen as a real endocrine body.<sup>4</sup>

## THE OSTEOCYTES AND THE BIOLOGY OF ORTHODONTIC AND ORTHOPEDIC MOVEMENT

In micro-bone lesions that occur daily, osteocytes die by apoptosis, such as when the bone tissue is dried and heated. The death of osteocytes in areas with 1-2 mm damage, such as microfractures, can generate mediators that stimulate clasts, especially RANKL,<sup>7</sup> a group TNF cytokine. Preserving the osteocytes is to prevent bone reabsorption and clinicians should know this information to take better care of the surgical margins in bone surfaces. In orthodontics many procedures are surgical.

An example of osteocyte preservation can be the divided flap technique in periodontal treatments, which preserves the periosteum attached on the surface. The source of nutrients in the bone are vessels of the periosteum. Preserving the periosteum means to keep alive the osteocytes so that its death does not induce the thin cortical alveolar bone resorption, leading to an undesirable dehiscence or fenestration.

Opening the periosteum inevitably leads to the death of the most superficial osteocytes, for they do not receive nutrients from broken vessels during this surgical procedure.

When the osteocytes die in bone remodeling tissue this area will inevitably be reabsorbed. Thus, the osteocytes should be preserved in the bony walls of the cavity prepared earlier to place the implants, avoiding excessive heat or improper manipulation of surfaces, since the death of osteocytes will lead to increased bone resorption at the site, which can disrupt osseointegration.

Probably some orthopedic facial responses can be explained by bone deformities produced. The responses controlled by the osteocytes can change the shape and size of the bone to adapt to new functional demands. This increasingly requires further studies.

More recently the sclerostin was discovered, a mediator secreted by osteocytes, that circulates the fluid spaces of bone, especially in tubules with cytoplasmic osteocites extensions.<sup>16</sup> It represents a regulatory molecule: If you need more bone, osteocytes release less sclerostin if you need to inhibit bone formation, osteocytes release more sclerostin.

The osteocytes seem to play a central role in bone remodeling.<sup>2</sup> On induced tooth movement there are bone deformations and deflections for each activation devices, especially in the interdental bone crest

and free surfaces. When moving a particular tooth to the lingual or buccal, it is known that on the outside, bone is deposited on the cortical surface.<sup>17</sup>

In induced tooth movement with biologically acceptable forces, probably the stimulus released by the network of osteocytes on the farther part of the ligament is of mediators in type and amount required for inducing bone formation, while in the periodontal surface of the alveolar bone, the osteocytes stimuli captured by the network lead to bone permeation of mediators that stimulate osteoclastogenesis and osteoclasia in the region.

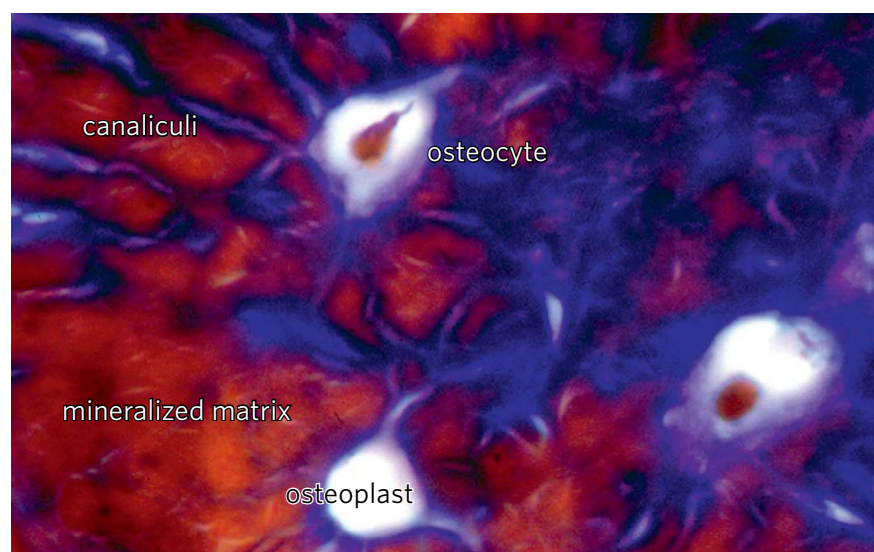
In turn, in the tooth movement induced by excessive force, the osteocytes die near the hyalinized ligament along one segment. Subjacent, the surviving osteocytes release mediators, which stimulate the underlying and peripheral osteoclastogenesis, as RANKL, while release more sclerostin to inhibit bone formation at the site. All these phenomena are occurring in the subjacent or adjacent hyalinized periodontal space, i.e., at a distance.

These discoveries in bone biology have led to search for new therapeutic alternatives for the bone metabolic problems. Some substances are death inhibitors of osteocytes on the skeleton as a whole and so promote less resorption, for example, estrogens and their modulators, bisphosphonates, calcitonin, CD40 ligand and others.<sup>2</sup> There are still anti-sclerostin

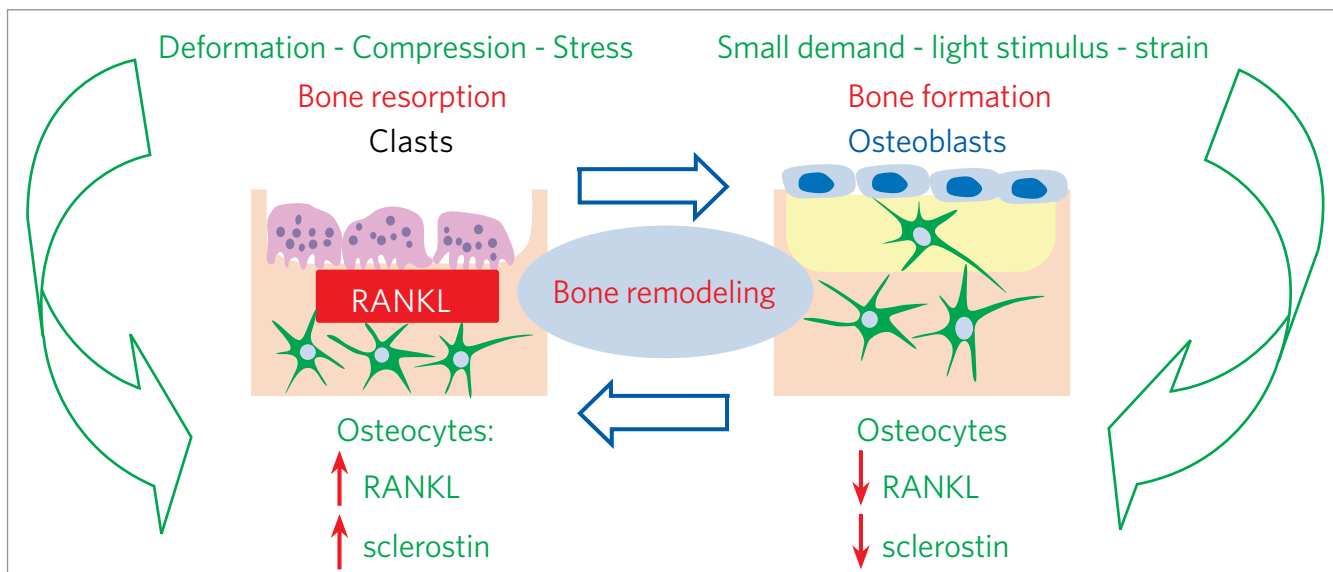
to help control bone loss in osteopenia and osteoporosis, the most common manifestations of various metabolic bone diseases.

## CONCLUSIONS

The osteocytes form a three-dimensional network with each cell communicating with other 40-50 by numerous cytoplasmic processes arranged like a real neural network. This communication is by cell contact and interaction, but particularly by mediators released by osteocytes in different amounts depending on the mechanical stimulus captured. Bone deformation by compression and



**Figure 2** - The osteocytes have many cytoplasmic prolongations, which intercommunicate with the mineralized matrix with other 20 to 40-50 cells and they detect minimal structural deformations and act as mechanotransducers. They occupy lacunae known as osteoplasts and the prolongations spread out as canaliculi, where mediators circulate in a tissue fluid, which performs ionic exchange with the mineralized extracellular matrix (Mallory, 100X).



**Figure 3** - The osteocytes detect shape and volume changes to increase or decrease the liberation of mediators involved in bone resorption or formation. In this manner, bone remodeling responds to the functional demand, modifying and adapting itself structurally (adapted from Nakasima et al,<sup>14</sup> 2011).

traction during orthodontic movement stimulates these mechanisms by mediators released by osteocytes that virtually controls the formation and resorption of bone surfaces.

To study the presence and specific effects of sclerostin, of RANKL and of osteoprotegerin in the biology of induced tooth movement may represent several insights in Orthodontics and Facial Orthopedics researches.

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