BONE MECHANOTRANSDUCTION AND ITS IMPLICATION IN THE PROCESS OF BONE REMODELLING

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ABSTRACT
Although bones seem inert, however, through the remodelling process, they constantly go through destruction and creation of bone tissue in relation with the mechanical forces that act on them. Bone mechanotransduction intervenes in the perception of the mechanical tensions that occur in the bone as a result of the action of various exterior mechanical forces and in their transformation in biochemical signals, so that the bone can react adequately. The present paper synthesizes recent aspects regarding mechanotransduction and bone remodelling, as well as the relation between them, both for the normal bone and for some pathological situations.

KEY WORDS: mechanotransduction, osteocytes, osteoclasts, bone remodelling

In order to optimally cope with the mechanical solicitations they are permanently submitted to, bones go through the remodelling process. Bone remodelling is a process that takes place without interruption through one’s life, and which refers to the reconstruction of the trabecular and cortical bone. The process starts with the bone resorption, followed by creation and deposition of new bone in the same place where resorption had taken place. Bone remodelling follows invariably the same scheme, which is different from that of modelling: activation→resorption→creation (Roblin et al., 2006). In the healthy bone, there is equilibrium between the quantity of resorbed bone and that of newly formed one.

THE BONE REMODELLING CYCLE
Remodelling is important for the repairing of the bone microdamage, for preventing the accumulation of an excessive quantity of old bone, and for mineral homeostasis. It is estimated that approximately 10% of the skeletal mass is annually renewed through this process. The spongy bone suffers remodelling more frequently than the compact bone, which explains why metabolic bone diseases like osteoporosis appear more often in bones with a bigger content of spongy tissue, such as vertebrae or hip bones (Lerner, 2006).

The cycle of bone remodelling consists of a series of events that can be grouped in a number of stages. Researchers such as Raisz et al. (1990) describe four stages of this process: the activation stage, which consists in the migration of preosteoclasts, which fuse to form osteoclasts, the resorption stage, in which the bone tissue is resorbed and, consequently, the resorption cavity is formed, the reversal stage, where mononuclear cells belonging to the macrophage line can be observed, and the formation stage, in which the cavity is filled with successive layers of osteoblasts, which produce the bone matrix. Other authors, such as Turner et al. (2001) and Pellene (2005), describe five stages of this process, by
adding to the ones already discussed a resting stage, in which a layer of inactive, flat osteoblasts cover the bone surface up until another remodelling cycle (Fig.1). Approximately 80% of the bone tissue is in this state.

![Figure 1. Schematic representation of bone remodelling (Tanna, 2005, with changes)](image)

**MECHANOTRANSDUCTION IN BONE**

The functional adaptation of bones is realized by the coordinated action of the osteoblasts and osteoclasts, which have to receive information regarding the local necessities of increasing or decreasing of bone tissue in accordance with the mechanical forces acting upon bones. The osteoblasts and the osteoclasts act on the surface of the bone tissue while the mechanical forces create tensions within the bone. Thus, changes in tension are detected by the osteocytes, which are spread in the entire matrix. However, it is not enough that they function as sensors; if the bone reaction to mechanical stimulation and its functional adaptation is to take place, the osteocytes need to communicate with the effector cells (Burger et al., 1995). There are researchers (Bonewald, 2006) who, while agreeing that the osteocytes constitute the majority type of mechanosensitive bone cells, credit the osteoblasts, as well, with a potential of mechanical sensitivity. Other researchers (McAllister et al., 2000) argue for the possibility that the osteoclasts possess this attribute, as well. Mechanotransduction is the process by which mechanical energy is converted into electrical or biochemical signals (Burger et al., 1999).

The bone can be likened to a rigid sponge full of liquid. Within it, the interstitial fluid in the mineralized matrix flows through the lacunocanalicular system of the bone (Tami et al., 2002). This flux from the lacunocanalicular system, with the influx at the level of the vascular system and the efflux in the lymphatic system, is essential for maintaining bones’ vitality, allowing osteocytes to receive nutrients and to eliminate the metabolism products (Knothe Tate, 2003). The effect of mechanical stimulation on the bone tissue intensifies the fluid flow from the canalicular network, which has the role of a physical mediator, stimulating the osteocytes. The liquid flow mechanically activates the bone cells,
but also transports the signaling molecules. The study of cell cultures has shown that the osteocytes in particular react to this liquid flow by a rapid release of nitric oxide and prostaglandins, which have the role of intercellular messengers and which help at recruiting osteoblasts and osteoclasts (Mullender et al., 2004). On the same lines, Burger et al. (1995) show that osteoblasts in culture react to physical stress by increasing the production of prostaglandins, especially PGE$_2$, and AMP$_C$. Chow et al. (1998) confirm that prostaglandins are necessary for inducing osteogenesis by mechanical stimuli, while inhibiting the production of prostaglandins and nitric oxide during the mechanical stimulation suppresses the osteogenetic response to mechanical stimulation.

The fluid flow that appears under the action of mechanical stimuli is usually oriented towards the periosteum. It is unlikely that the signaling molecules elaborated by osteocytes and osteoblasts could diffuse against this flow towards the osteoclasts situated at the level of the endosteum. This has determined some of the researchers to consider that the osteoclasts are also sensitive to the liquid flow and that the activity of the osteoclasts in the remodelling process is controlled by autocrin factors (Mc Allister et al., 2000).

These phenomena, which take place in the bone and which consist in the bone adapting to different mechanical forces acting upon it, have been compared with those that take place in the blood system, more specifically with the adaptation of the blood vessels to changes in the blood flow. An enhancement in blood circulation, like, for example, during physical effort, leads to vasodilation. The endothelial cells have the role of mechanical sensors, sensitive to the enhancement of blood flow, which releases the same intercellular mediators, that is nitric oxide and prostaglandins. These messengers determine the relaxation of the flat muscle cells from the vascular walls, thus allowing for vasodilatation to occur. Endothelial cells have the capacity to produce nitric oxide when they are in the presence of a specific enzyme, endothelial NO synthase. This enzyme has been identified in human bone cells cultures, as well. Thus, it seems that the endothelial cells and the osteocytes have a similar sensory system for the fluid flow and that both types of cells function as efficient sensors of the fluid flow (Mullender et al., 2004).

The mechanotransduction includes a number of stages (Burger et al., 1995). First, the mechanical stress is converted into physical signal, representing the mechanical coupling; then, the physical signal is transformed, at the level of the mechanosensitive cell, in biochemical signal, representing the biochemical coupling; at last, the biochemical signal is transmitted to the effector cells, the osteoclasts and the osteoblasts, which will react by reducing or increasing the bone matrix in a certain place. Ruimerman et al. (2005) think that the coupling factor between the osteoclastic bone resorption and the osteoblastic osteogenesis has a mechanical nature. Thus, the resorption cavity produces stress concentration around itself, as a result of changes in forces transmission within the bone. This will intensify mechanical signals which are transmitted to the osteocytes, which will determine the recruitment of osteoblasts. The osteoblasts, in their turn, will be
in osteogenetic activity until the filling of the cavity. Moreover, as Burr (2004) shows, the stress concentrations determined by the resorption cavities can lead to microfractures.

The activity of osteoclasts and osteoblasts which define the bone remodelling takes place simultaneously in a number of locations in the skeleton, within the so called basic multicellular units or bone metabolic units (BMU), where bone destruction and bone creation alternate closely. Harold Frost (1964) is the one who defined the basic multicellular unit and who showed that it is an essential factor for bone metabolism (Turner et al., 2004).

The osteoclast mass within the BMU resorbs the bone tissue and creates a cutting cone, which represents the leading pole of this structure, and is followed by osteoblasts, which centripetally deposit layers of new bone tissue, in order to fill the tunnel excavated by osteoclasts, and which constitutes the closing cone. The concentric deposition of bone tissue stoppes and leaves a central space, which is the future Haversian canal in the newly formed osteon (Roblin, 2006). The BMU is a temporary structure which advances by the activity of the osteoclasts, which remove the matrix by acidification and proteolytic digestion, followed by the osteoblasts, which migrate to the excavated region where they start the osteoformation process by secretion of osteoid, which will afterwards be mineralized. In the healthy human bone, 3-4 millions BMU are formed every year, and 1 million BMU are permanently active (Manolagas, 1999). As Couret, (2004) shows, the life span of a BMU is 6 to 9 months, a period in which osteoclasts and osteoblasts are permanently recruited.

The remodelling of the spongious bone follows the same sequence of cellular events as the compact bone, but the advancement of the BMU happens through the excavation of a channel at the level of the resorption surface, rather than by the excavation of a tunnel, as it is the case with the compact bone. This can be visualized as a hemiosteonal remodelling, as opposed to the osteonal remodelling that takes place in the case of the compact bone, as Parfitt (2004) has shown.

A negative balance at the level of the basic multicellular unit or an increased remodelling rate or both have bad consequences on the solidity and resistance of bones. During the increase of the bones within the BMU, the newly synthesized bone volume surpasses the one being resorbed, so that every reiteration of the cycle adds a surplus of bone. When the skeleton has reached the genetically programmed dimensions, the remodelling rate reduces, and osteogenesis and osteolysis reach a balance. With growing age, there is a decline of osteoformation in relation to the resorption; this unbalances the two processes and bone loss takes place. At the level of each BMU, the net bone formation during development and the net bone loss after maturity are small. That is why, the bone formation rate during development and, respectively, the bone loss after maturity are determined by a high remodelling rate rather than by the amplitude of the disequilibrium within the basic multicellular unit.
A rapid remodelling rate (regardless of the disequilibrium within the BMU) represents an increased risk of fractures for more reasons. First of all, it concerns the replacement of a highly mineralized bone with a younger bone, less mineralized, and thus resistance decreases. Secondly, the resorption lacunae stay temporarily unfilled by newly formed bone tissue (there is a gap between resorption and formation), and this predisposes the bone to microdamage production. Thirdly, the accentuated remodelling impairs the collagen maturation and isomerization, increasing bone fragility (Seeman et al., 2006). The same author shows that bone tissue loss within each BMU determines narrowing of the cortical bone, intracortical porosity especially near the bone marrow, trabecular narrowing, complete trabecular destruction and loss of intertrabecular connectivity.

As Martin (2002) shows, older conceptions on bone remodelling claim that this process takes place mainly for metabolic purposes, like assuring calcium homeostasis. However, lately, another theory has been gaining ground, according to which bone remodelling is initiated by the existence of bone tissue microdamages, which are removed as the remodelling process develops.

On these lines, research carried by Burr et al. (1985) confirms that microdamage caused by fatigue represent a significant factor for the initiation of intracortical remodelling. Mori et al. (1993) prove that bone remodelling preferentially occurs in regions with microdamage caused by fatigue and that there is direct, cause-effect relation between the appearance of the microdamage in the bone and its repairing. The research carried by Lee et al. (2002) supports the theory that bone microdamages are stimuli for the initiation of the remodeling process.

The bone has an operation threshold of microdamage. If bone tensions and deformations are below this threshold, the remodelling units can repair the microdamage; if the tensions are above this threshold, they determine microdamages that surpass the possibility of repairing of the bone tissue and which, in time, will accumulate and will cause non-traumatic fractures (Frost, 2003).

Bone remodelling ensures the adequate relation between the quantity and spatial organization of the bone tissue and the different types and intensities of mechanical forces that act upon it, and thus the functional adaptation of bones is achieved. As Ruimerman et al. (2005) have shown, the mass and the form of bones is the resultant of osteoclastic resorption and osteoblastic osteoformation, modulated by external mechanical solicitations through the stimulating and signaling of the osteocytes.

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