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Mechanobiology of bone tissue

Mecanobiologie du tissu osseux

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Abstract

In order to obtain bones that combine a proper resistance against mechanical failure with a minimum use of material, bone mass and its architecture are continuously being adapted to the prevailing mechanical loads. It is currently believed that mechanical adaptation is governed by the osteocytes, which respond to a loading-induced flow of interstitial fluid through the lacuno-canalicular network by producing signaling molecules. An optimal bone architecture and density may thus not only be determined by the intensity and spatial distribution of mechanical stimuli, but also by the mechanoresponsiveness of osteocytes. Bone cells are highly responsive to mechanical stimuli, but the critical components in the load profile are still unclear. Whether different components such as fluid shear, tension or compression may affect cells differently is also not known. Although both tissue strain and fluid shear stress cause cell deformation, these stimuli might excite different signaling pathways related to bone growth and remodeling. In order to define new approaches for bone tissue engineering in which bioartificial organs capable of functional load bearing are created, it is important to use cells responding to the local forces within the tissue, whereby biophysical stimuli need to be optimized to ensure rapid tissue regeneration and strong tissue repair.

Résumé

La masse osseuse et son architecture s'adaptent en permanence aux contraintes mécaniques environnantes, afin de conférer à l'os une résistance appropriée à la rupture en utilisant le moins de matière possible. Il est couramment admis que cette adaptation est sous le contrôle des ostéocytes, qui répondent aux flux de liquide interstitiel induits par les contraintes mécaniques à travers le réseau lacuno-cunaliculaire en produisant des molécules de signalisation. Densité et architecture osseuses optimales ne dépendent pas seulement de l'intensité et de la distribution spatiale des stimuli mécaniques, mais aussi de la capacité de réponse des ostéocytes à ces stimuli. Les cellules osseuses sont réactives vis-à-vis des stimuli mécaniques, mais les paramètres des contraintes qui jouent un rôle critique restent mal connus. De même ne sait-on pas si différentes modalités de contrainte telles que cisaillement, tension ou compression affectent les cellules différemment ou non. Ainsi et bien qu'une déformation des tissus, et des contraintes de cisaillement induites par le fluide interstitiel entraînent une déformation des cellules, ces stimuli pourraient enclencher différentes voies de signalisation impliquées dans la croissance et le remodelage osseux. La mise au point de nouvelles approches d'ingénierie tissulaire permettant l'élaboration d'organes bioartificiels capables de subir des contraintes mécaniques, requiert à la fois l'utilisation des cellules à même de répondre aux forces locales s'exprimant au sein des tissus, et l'optimisation des stimuli biophysiques à appliquer pour favoriser une régénération rapide des tissus et la solidité des tissus régénérés.

Keywords: Bone cells; Fluid shear stress; Mechanotransduction; Bone formation; Bone resorption

Mots clés : Cellules osseuses ; Contraintes de cisaillement ; Mécanotransduction ; Ostéogenèse ; Résorption osseuse

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1. Bone remodeling and mechanosensitivity of osteocytes

Bone is a living tissue that is remodeled throughout life by bone resorbing osteoclasts and bone forming osteoblasts. Under normal conditions, bone resorption and bone formation are intimately linked processes that always occur in the same sequence and are executed by a group of osteoclasts and osteoblasts that form the so-called basic multicellular unit (BMU). Osteoclasts start resorbing bone in response to as yet undetermined signals that may relate to local damage [1] and/or osteocyte death [2]. In response to a coupling signal [3], osteoblasts are recruited to deposit bone matrix, which is later mineralized. The exact nature of the coupling signal is still unclear, but likely relates to local strain levels [4,5]. Remodeling allows bone tissue to adapt its internal structure and mass to mechanical demands (functional adaptation) to ensure maximal strength with minimal bone mass. Apart from mechanical demands, the rate of bone remodeling and the activity of bone cells are mainly regulated by hormones such as estrogen and parathyroid hormone.

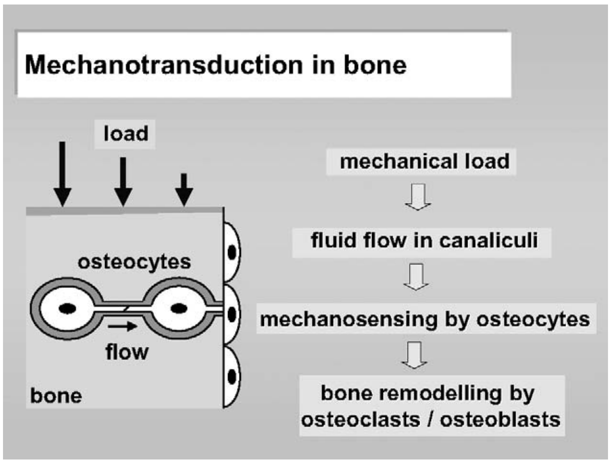

Fig. 1. Model for the transduction of mechanical strain to osteocytes in bone. Left: The osteocyte-lining cell network of a piece of bone tissue under stress (large arrows). Loading results in flow of interstitial fluid in the canalicular non-mineralized matrix (horizontal arrow).

During remodeling, alignment of new bone is along the dominant local loading direction, suggesting local regulation of bone formation by mechanical stimuli [6]. It has become clear over the last several years that the osteocytes are the professional mechanosensory cells of bone, and the lacuno-canalicular porosity the structure that mediates mechanosensing [7]. It has been shown that mechanical load induces fluid flow in the canalicular network [8]. This fluid flow has been suggested as a physical mediator of mechanosensing by osteocytes in vivo [9]. The osteocytes respond to mechanical stimuli with the production of signaling molecules which modulate the activities of osteoblasts and osteoclasts, thus converting mechanical stimuli into cellular signals [10] (Fig. 1).

Osteocytes, having a typical morphology with long slender cell processes (Fig. 2), form a network throughout the bone matrix, and are thought to respond to opposite strain fields occurring in a BMU [11]. They facilitate osteoclastic activity in front of the cutting cone, where strains are low, and stimulate osteoblastic bone formation around the closing cone, where strains are high. Osteoclast and osteoblast activity could thus be related to opposite strain modalities, whereby mechanosensitive osteocytes orchestrate the activities of these cells in the remodeling process [4,5].

2. Mechanical stimulation of bone cells by fluid flow

Bone cells respond to fluid flow stimulation in vitro [12–20]. By comparing variations in fluid transport with variations in wall shear stress, we have shown that the flow-derived stimulus that activates the bone cells is shear stress rather than streaming potentials or chemotransport [20]. Fluid shear stress plays an important role in normal physiology, such as in the adaptation of blood vessels to changes in blood

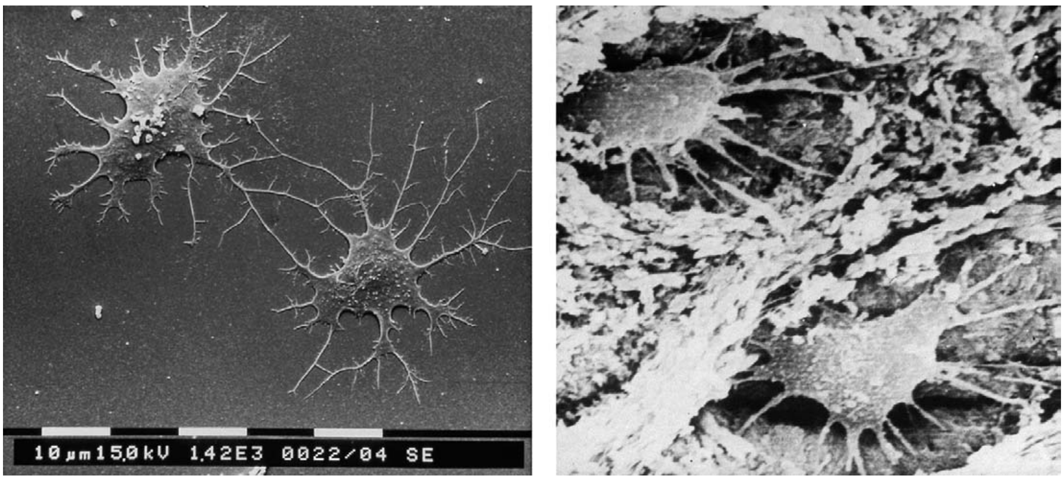

Fig. 2. Osteocyte morphology. Left: Isolated osteocytes in culture. Osteocytes were isolated by an immunodissection method using MAb OB7.3-coated magnetic beads. After isolation the cells were seeded on a glass support, cultured for 24 h and studied with a scanning electron microscope. After attachment, osteocytes form cytoplasmic extrusions in all directions. Right: Osteocytes embedded in calcified bone matrix. Note the many cell processes, radiating from the osteocyte cell bodies, as visualized using scanning electron microscopy. Magnification: 1000×.