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Commentary

Mechanotransduction in osteoclasts: Novel strategies of bone repairs

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ABSTRACT

Mechanotransduction, the transfer of mechanical stimuli into various biological signals, is a vital biological process in multiple organ systems. The osteoclast (OC) plays a vital role in bone metabolism and repair. The role of mechanotransduction in osteoclasts and other bone cells is emerging. This commentary highlights a recent research report on a novel strategy for the precise regulation of OC formation via modulating matrix stiffness. Modulation of the mechanotransduction pathways in the skeletal system will pave the way for the development of a matrix stiffness-based strategy for bone tissue regeneration.

1. Commentary

The osteoclast (OC) plays a vital role in bone metabolism and repair. Its dysregulation can lead to diseases of either bone thinning or thickening. Osteoporosis (OP), i.e. low bone mass associated with increased fragility, results from a failure of the critical balance between bone formation and resorption, controlled by interaction between osteoblasts (OB) and OCs [1,2]. Abnormal OC function can disrupt bone remodeling and manifest in osteolytic bone diseases such as aseptic loosening of prosthetic joint replacements, osteoporosis, and rheumatoid arthritis, etc. [3,4]. Current clinical strategies for osteolytic conditions have focused on the modulation of biochemical signalling molecules in s, including specific antibodies to RANKL (Denosumab), the key cytokine for OC formation and bone resorption, and other anti-resorptive agents like bisphosphonates [5]. However, issues remain including compliance and adverse effects (e.g. rebound vertebral fracture, osteonecrosis of the jaw, and atypical sub-trochanteric femoral fractures) [6]. Furthermore, bone fragility fractures in the elderly lead to increased mortality rates [7]. Identification of new ways to control OC will lead to the gain of new knowledge and a breakthrough in treatment for bone regeneration.

Mechanotransduction, the transfer of mechanical stimuli into various biological signals, is a vital biological process in multiple organ systems [8,9]. In the skeletal system, mechanotransduction is essential to bone mass, strength, and shape. Bone cells use mechanotransduction to sense and convert mechanical stimuli into a set of biochemical reactions and cellular responses that result in intracellular changes, such as activation of signaling cascades, cytoskeleton structures, ion concentrations, and transcriptional regulation [10,11]. For instance, PIEZO1 and microRNA-103a were identified to mediate skeletal mechanosensory regulation [12,13].

The molecular basis by which OCs are directly regulated by mechanotransduction remains to be defined. Interestingly, in this study, the modulation of the strength of the hydrogel matrix was found to mediate OC differentiation and bone resorption in the bone microenvironment. A team led by Academician Liu Changsheng of the East China University of Science and Technology investigated a key hypothesis that mechanical stimulation may serve as a potential strategy to manipulate the physiological bone microenvironment with stiffness [14]. To this end, they generated hydrogels with various stiffnesses ranging from 2.43 kPa to 68.2 kPa, and examined the effect of matrix stiffness on OC fate. Their results demonstrated that matrix stiffness could be used to guide OC behaviour. Notably, increased matrix stiffness was found to promote osteoclastogenesis via attenuating integrin β3-sensitive RhoA-ROCK2-yap-associated mechanotransduction. In addition, the hydrogel with a medium stiffness (17.5 kPa–44.6 kPa) was found to enhance vascular remodeling and bone regeneration of bone defects in mice. This study explores an innovative approach to fine-tune OC differentiation via integrin-dependent mechanotransduction, which will facilitate to development of an optimal matrix stiffness-based bone tissue engineering strategy.

The investigators generated GelMA hydrogel through the reaction of gelatin and methacrylate to investigate how the stiffness of the matrix affects OC behavior. H-gel had a stiffness of 68.2 kPa with cross-linking 30% GelMA content for 90 S; M-gel had a stiffness of 29.4 kPa with cross-linking 20% GelMA content for 90 S; and S-gel had a stiffness of 2.43 kPa with cross-linking 10% GelMA content for 30 S. They showed that

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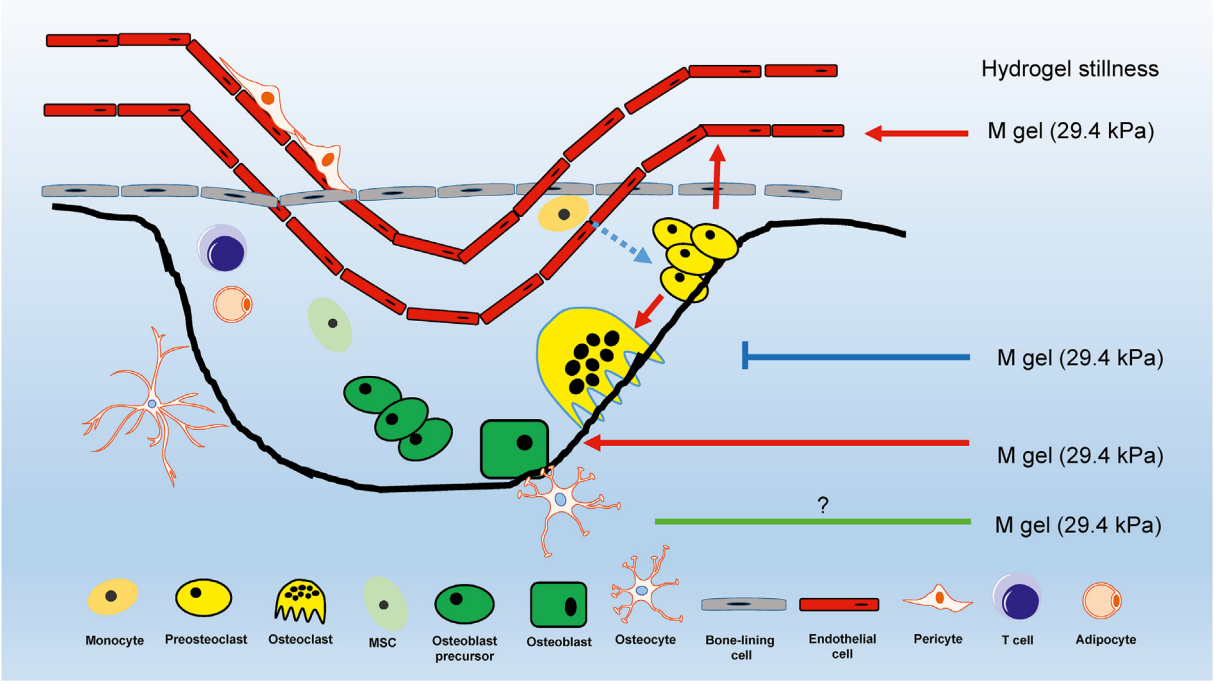

Fig. 1. A working model of hydrogel stiffness on cells of the basic multicellular unit (BMU) [22]. M-gel (29.4 kPa) was found to promote angiogenesis and osteogenesis through preosteoclasts with reduced osteoclast activity. In comparison, hydrogel stiffness from 10.4 kPa to 29.4 kPa led to an increase in osteoclast number, and hydrogel stiffness from 29.4 kPa to 68.2 kPa resulted in the increased size of osteoclasts (14). The direct effects of hydrogel stiffness on mesenchymal stem cells (MSC), osteocytes, pericytes, and other cells in the bone microenvironment are yet to be elucidated.

hydrogels with different stiffnesses have good cytocompatibility, and the cells were able to maintain a similar metabolic activity in all hydrogel groups. Next, they evaluated the effect of various hydrogel stiffness on OC differentiation and found that hydrogel stiffness influenced OC number and size. An increase in the number of OCs was found with a significant increase in hydrogel stiffness from 10.4 kPa to 29.4 kPa and with no significant difference in hydrogel stiffness from 29.4 kPa to 68.2 kPa. In comparison, the size of OCs increased significantly in hydrogel stiffness from 29.4 kPa to 68.2 kPa. Matrix stiffness was also found to regulate osteoclastic bone resorption. OCs in the H-gel group with an increase in matrix stiffness were found to promote OC-mediated bone resorption as shown by scanning electron microscopy and by the increased levels of CTX-I. Interestingly, H-gel was found to induce the expression of integrin β3, inactivate the RhoA signaling pathway, and regulate OC formation via mechanotransduction pathways. They showed that the expression of integrin β3 and ROCK1 was significantly increased in hydrogel stiffness accompanied by reduced signaling of RhoA and ROCK2, and myosin II. H-gel was also found to weaken mechanosensation and promotes NF-κB signaling, suggesting that RhoA is upstream of NF-κB signaling pathway and plays a role in matrix stiffness-mediated osteoclastogenesis.

Intriguingly, M-gel was found to promote bone regeneration with reduced OC activity. In this experiment, distal femoral defects were employed to investigate the effect of S-gel, M-gel, and H-gel on matrix stiffness-mediated osteoclastogenesis, osteogenesis, and angiogenesis in mice. Consistently, the M-gel group had more bone regeneration with increased bone volume per tissue (BV/TV), trabecular thickness (Tb, Th), and trabecular number (Tb, N) measured by μCT when compared with other groups. The higher the stiffness of the hydrogel, the higher the expression levels of OC-related and mechanotransduction-related mRNAs. Increased hydrogel stiffness led to more TRAP-positive OCs, whereas more mononuclear preosteoclasts were observed in M-gel than in other groups, indicating that M-gel effectively hindered the fusion of preosteoclasts and enhanced the maintenance of preosteoclasts. Taken together, these results indicated that M-gel promoted bone formation at bone defect sites with reduced OC activity.

Additionally, M-gel was also found to promote angiogenesis and osteogenesis through preosteoclasts. It was revealed that the M-gel group had the most $Emcn^{high}CD31^{high}$-stained blood vessels, higher than those in the S-gel and H-gel groups. Similarly, osteoblast progenitor cells were induced in the M-gel group as compared with S-gel group and H-gel group. These results are in line with the concept of angiogenesis and osteogenesis coupling and verse versus [15–17]. Mechanistically, hydrogels mediate the formation of preosteoclasts through integrin-involved RhoA-RoCK2-yap-mediated mechanotransduction and NF-κB-mediated biochemical transduction, which is in company with enhancing angiogenesis and osteogenesis, leading to promoting bone repair.

In summary, mechanotransduction has a meaningful impact on skeletal function via a variety of mechanical loads. For example, appropriate exercise has been found beneficial to bone health [18,19]. It is anticipated that the transmission of biomechanical forces into multiple cellular signals involves integrins, adhesion molecules, cell surface receptors, cytoskeleton, and ion channels [20,21]. Novel strategies on how to precisely regulate OC differentiation are of great interest. In this study, through modulating matrix stiffness, the team identifies an innovative way to regulate osteoclastogenesis [14]. Increased matrix stiffness was found to promote osteoclastogenesis by inhibiting integrin-mediated mechanotransduction. On the other hand, a matrix with similar vascular stiffness could lead to increased preosteoclast formation, vascular remodeling, and bone regeneration (Fig. 1). It will be interesting to see if various matrix stiffness affects osteoblasts and osteocytes similarly. This commentary highlights a recent report on a novel strategy for the precise regulation of OC formation via modulating matrix stiffness, which will pave the way for the development of a matrix stiffness-based strategy for bone tissue regeneration. Thus, modulation of the mechanotransduction pathways in the skeletal system could enable novel treatment strategies for bone diseases.

Declaration of interest statement

I have no conflict of interest.

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