PRACA POGLĄDOWA

Role of osteoblasts and osteocytes in bone remodeling

Rola osteoblastów i osteocytów w procesie przebudowy kości

Urszula Cegieła, Hanna Korzeniowska, Agnieszka Wilk

ABSTRACT

Bone remodeling is an integrated process of resorption and osteogenesis. Such processes are performed on cyclical basis, as regulated by specific bone cells, including osteoclasts, osteoblasts and osteocytes. Not long ago it was claimed that bone remodeling involves only osteoclasts, conditioning bone resorption and osteoblasts, responsible for osteogenesis. Recent studies have shown however, that the major regulatory part in bone remodeling is taken by osteocytes. Such cells regulate the activity of osteoclasts and osteoblasts, influencing the RANK/RANKL/OPG pathway as well as the signalling canonical pathway Wint/β-catenine. The role of osteocytes in regulation of RANK/RANKL/OPG pathway is basically associated with regulation of RANKL secretion by osteoblasts, while in regulation of Wnt/ /β-catenine, with secretion of sclerostin, which inhibits osteogenesis by blocking activation, proliferation and differentiation of osteoblasts from the mesenchymal stem cells and slows down Wnt/β-catenine signalling.

KEY WORDS
osteoblasts, osteocytes, bone remodeling, RANK/RANKL/OPG pathway, Wnt/β-catenine pathway, sclerostin

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STRESZCZENIE

Aktywność metaboliczna szkieletu związana jest z ciągłą przebudową tkanki kostnej. Mechanizm ten jest niezbędny do przystosowania szkieletu do warunków zewnętrznych i obciążeń mechanicznych oraz zapewnia równowagę mineralną. Prawidłowy przebieg procesu przebudowy kości zależy od aktywności komórek kostnych, do których należą osteoblasty, osteoklasty i osteocyty.
Osteoblasty uczestniczą w kościotworzeniu oraz resorpcji kości. Wydzielają cytokiny i czynniki wzrostu, dzięki czemu pełnią rolę regulacyjną procesu osteoklastogenezy i resorpcji kości przez wpływ na szlak regulacyjny RANK/RANKL/OPG. Osteocyty z kolei regulują osteoblastogenezę, proces apoptozy osteoblastów oraz funkcję szlaku RANK/RANKL/OPG

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przez wpływ na kanoniczny szlak sygnalizacyjny Wnt/β-katenina. Osteocyty wydzielają również sklerostynę, działającą antagonistycznie w stosunku do szlaku kanonicznego WNT/β–katenina. Sklerostyna hamuje proces kościotworzenia. Szlak Wnt/β–katenina może być potencjalnym celem terapii, prowadzącym do zwiększenia masy kostnej, natomiast sklerostyna – jako inhibitor tego szlaku – stanowi nowy obiecujący cel w badaniach nad terapią anaboliczną schorzeń tkanki kostnej.

SŁOWA KLUCZOWE
osteoblasty, osteocyty, przebudowa kości, szlak RANK/RANKL/OPG, szlak Wnt/β–katenina, sklerostyna

Bone tissue remodeling preserves the bone mass, adapts the skeleton to the changing external conditions and mechanical loads, and is responsible for repair of microfractures as well as mineral homeostasis of the body. It appears as an integrated process of resorption and osteogenesis. Such processes are triggered on cyclical basis and their activity peaks upon the body growth and upon mechanical damages of bones. Proper course of reconstruction is dependent on activity of specific bone cells, including osteoclasts, osteoblasts and osteocytes [1,2]. All bone cells involved in remodeling form the basic multicellular unit (BMU). Moreover, the role of bone cells in remodeling patterns is not restricted to resorption and osteogenesis. Such cells secrete also the growth factors as well as cytokines conditioning regulation of the remodeling process [1,3,4].

The major part in bone tissue remodeling is taken by RANK/RANKL/OPG pathway, now well described in literature [5,6]. The main regulator of this pathway is RANKL cytokine – receptor activating the nuclear factor κB (RANK) ligand. RANKL cytokine is the key factor to determine differentiation and resorption activity of osteoclasts as well as suppressing apoptosis of mature osteoclasts. Differentiation of osteoclasts requires also a macrophage colony-stimulating factor (M-CSF), to initiate osteclast differentiation from precursor cells M-CSF performs through the membrane receptor with tyrosine kinase activity, situated on osteoclast precursor cells in the monocyte-macrophage line. Further differentiation, induced by RANKL leads do creation of resorptionally active osteoclasts. RANKL stimulates RANK membrane receptors which belong to the superfamily of tumor necrosis factor receptors, found on the surface of osteoclast precursor cells. Stimulated by RANKL, RANK receptors activate κB nuclear factor which transmits a signal to the cell nucleus to activate expression of genes responsible for differentiation of osteoclast precursors to osteoclasts. Activating κB nuclear factor, RANKL not only conditions differentiation but also the resorption activity of mature osteoclasts as well as inhibition of their apoptosis [6,7,8,9].

The resorption activity and apoptosis of osteoclasts are also controlled by osteoprotegerin (OPG) which is a receptor protein in the tumor necrosis factor receptor superfamily. OPG contains no transmembrane domain. It is a soluble receptor binding the RANK ligand. Binding RANKL, it suppresses formation and resorption activity of osteoclasts and inhibits osteoclastogenesis and bone resorption [10,11].

Similarly to mature osteoclasts, osteoclast precursor cells do not synthesise RANKL. Neither do they synthesise M-CSF or OPG. Both, RANK ligand and M-CSF as well as OPG are synthesized by osteoblasts and bone marrow stromal cells. Osteoblasts appear then indispensable to initiate differentiation and formation of active osteoclasts. Secreting OPG, they simultaneously block RANKL effect and inhibit osteoclastogenesis. Such dual role of osteoblasts ensures strict control of the osteoclast functions by osteoblasts as well as bone resorption regulation, necessary then to ensure a proper remodeling course [5,7,12].

Not long ago it was claimed that remodeling involves only osteoclasts, conditioning bone resorption, and osteoblasts responsible for osteogenesis. Osteocytes were then considered inactive. Recent studies have pointed however to osteocytes playing key regulatory role in bone remodeling. Absence of such cells effects in mechanotransductive failure, intensified bone resorption and reduced mineralization which in turn leads to microfractures of the

bone tissue, weakened mechanical properties and lower strength [13,14]. The studies showed that osteocytes are active cells. What is more, without the role of osteocytes, proper bone remodeling and performance of the skeletal system are not possible.

Osteocytes are formed from osteoblasts and share approximately 90% of osseous cells while their lifetime ranges between 10 and 20 years. Compared to osteoclasts, which perform only upon resorption lasting for 2–3 weeks, or osteoblasts which build a new bone during 2–3 months, osteocytes are the longest living line of bone cells. Communication between osteocytes and the bone surface as well as other bone cells is ensured through a network of canaliculi [13,15]. The role of osteocytes in regulation of RANK/RANKL/OPG pathway is associated first of all with regulation of RANKL secretion by osteoblasts. Absence of osteocytes effects in RANKL overproduction by osteoblasts and increased bone resorption [6]. Osteocytes regulate also apoptosis of osteoblasts as well as function of RANK/RANKL/ /OPG pathway, influencing the canonical signalling pathway Wnt/β-catenine [6,18,19].

The canonical pathway Wnt/β-catenine plays an important part in preserving bone tissue homeostasis. It is indispensable upon osteoblastogenesis and osteogenesis. With role of secretion proteins of Wnt (Wingless) family, it transmits the intracellular signals. The coreceptors of Wnt proteins are transmembrane proteins LRP-5 and LRP-6 (low density lipoprotein receptor-related protein 5 and 6) of low density lipoprotein family. Wnt proteins transmit the intracellular signal via Fzd (Frizzeled) membrane receptor. Binding Wnt proteins with Fzd receptor activates canonical signalling pathway Wnt/β-catenine with β-catenine performing as the central proteine [20,21,22,23].

At no effect of Wnt proteins with Fzd receptor, the Wnt/β-catenine pathway is inactive and β-catenine binds in the complex with APC (adenomatous polyposis coli) protein, axin, conductin, 3β glycogen synthase kinase (GSK-3β) and cazeine kinase-1α to become degradated [21].

Wnt proteins transmit the intracellular signal provided the Wnt-Fzd complex is bound by LRP-5 coreceptor and Dvl cytoplasmatic protein (Dishevelled) activated. Subject to phosphorylation and activation, Dvl protein binds then with β-catenine docking APC/axin/conductin complex, while the intracellular domain of LRP-5 coreceptor binds axin. Such processes effect in suppressed activity of GSK-3β and cazeine kinase-1α, responsible for β-catenine phosphorylation which prevents its proteasomal degradation. In consequence of blocked phosphorylation, free β-catenine accumulates in the cell to translocate then to the nuclear where complexes with the transcription factors (Tcf/Lef) are formed. Such a transcription complex induces expression of genes dependent on Wnt which are responsible for regulation of the cellular cycle, apoptosis and proliferation. Expression of those results in production of c-Myc transcription factor, which is needed for the cells to pass from phase G1 to S of the cellular cycle and for the stem cells to quit the undifferentiated state [6,22,24,25].

The canonical signalling pathway Wnt/β-catenine performs in all cells of the osteoblastic line, including prosteoblasts, the lining cells and osteoblasts. It plays the central role in development of osteoblast precursors, originating from bone marrow mesenchymal cells. Activation of the canonical regulation pathway Wnt/β-catenine through LRP-5 stimulates formation, proliferation and differentiation of osteoblasts from the precursor cells, stimulates functions of osteoblasts and suppresses apoptosis. LRP-5 is also essential for anabolic performance of PTH and acts as a mediator while mechanical load is imposed on the bones. The data available show that Wnt/β-catenine pathway and PTH stimulate osteogenesis through complementary routes. Mutations reducing the LRP-5 function effect in development of osteoporosis while those enhancing the LRP-5 function result in high bone mass phenotype. Additionally, Wnt proteine stimulate osteoblastogenesis. It was proved that elevated Wnt10b concentration in the bone marrow cell colony was proportional to the growth of Osterix and Runx2 transcription factors. Runx2 transcription factor is the superordinate regulator of osteogenesis. It controls proliferation, growth as well as differentiation of mesenchymal stem cells into mature osteoblasts, while Osteric regulates differentiation of progenitor cells into osteoblasts, and its expression depends on Runx2 [6,16,17,20,23].

The Wnt/β-catenine pathway regulates also bone resorption through blocked osteoclastogenesis. Blocking of osteoclastogenesis is due to activation of the canonical signalling pathway Wnt/ /β-catenine in osteoblasts via LRP-6. Osteoclas-

togenesis is blocked indirectly through activation of osteoblasts and increased OPG/RANKL ratio. It has been shown that mutations of LRP--6 gene effect in stronger osteoclastogenesis and resorption activity of osteoclasts which consequently leads to larger surface of erosion and reduced bone mass [16,18].

The major regulators of Wnt/β-catenine pathway and of the bone remodeling process are osteocytes. Mature osteocytes secrete sclerostin which is antagonist of the canonical pathway Wnt/β-catenine. Sclerostin suppresses osteogenesis through blocked activation, proliferation and differentiation of osteoblasts from the mesenchymal stem cells. It slows down Wnt/β-catenine signalling, binding with LRP-5 and LRP-6 coreceptors. Osteoblasts lacking β-catenine show higher RANKL expression and reduced expression of OPG. Moreover, sclerostin blocks also BMP-induced osteogenesis. Sclerostin binds the BMP responsible for activation of osteoblastogenesis, inducing expression of alkaline phosphatase and osteocalcin as well as Osterix and Runx2 transcription factors [16,19].

Expression of sclerostin depends on the mechanical effect imposed on the bone and is regulated by osteocytes. Responding to the detected mechanical stress and microfractures, the cells reduce sclerostin expression to activate Wnt/β-catenine signalling. Activation of the canonical regulation pathway Wnt/β-catenine through LRP-5, stimulates proliferation and differentiation of osteoblasts from precursor cells, stimulates the function of osteoblasts, suppresses apoptosis and finally enhances the mass and strength of bones through stimulation of osteogenesis. Activation of the signalling pathway Wnt/β-catenine by osteocytes appears then as a physiological response to any mechanical load. Moreover, the pathway has a role in healing of fractures [19,21,24,25,26]. Investigation carried out throughout a few past years indicated that the signalling pathway Wnt/β-catenine may be a potential target of therapy to ensure growth of the bone mass, while sclerostin, as the major inhibitor of Wnt/β-catenine pathway, could appear as a new promising target of research into anabolic therapy in bone tissue diseases, leading to reduction of the bone tissue and lower resistance to fractures. Present studies focus on humanized monoclonal antibodies blocking the effect of sclerostin [6,16,18,19].

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