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BONE REMODELING IN NORM AND IN PRIMARY OSTEOPOROSIS: THE SIGNIFICANCE OF BONE REMODELING MARKERSS

Abstract

Osteoporosis is a systemic skeletal disease is characterized by low bone mass and microarchitectural deterioration of bone tissues, leading to fragility fractures. The number of patients with osteoporosis is steadily increasing due to the aging of society. Osteoporosis is an extremely common disease: it affects more than 200 million people worldwide and causes more than 8.9 million fractures. In Russia, among people aged 50 years and older, osteoporosis is diagnosed in 34% of women and 27% of men. The social significance of osteoporosis is determined by its consequences: fractures of bones of the peripheral skeleton and vertebral body fractures, leading to high material costs and causing a high level of disability and mortality. The normal physiological process of bone remodeling involves a balance between bone resorption and bone formation. In osteoporosis, this process becomes unbalanced, resulting in gradual losses of bone mass and density due to enhanced bone resorption and/or inadequate bone formation. Several signaling pathways underlying primary osteoporosis have been identified, such as the osteoprotegerin/receptor activator of nuclear factor kappa-B (RANK) / RANK ligand (RANKL), bone morphogenetic proteins, canonical Wnt-signaling pathway. In addition, genetic disorders are involved in the development of the pathogenesis of osteoporosis. To identify osteoporosis, WHO recommends the use of dual energy X-ray absorptiometry, which allows you to study the quantitative characteristics of bone tissue. Currently, there are various methods for evaluation of the quality of bone (microarchitectonics, the ability of bone tissue to be resistant to fracture), but these methods have limitations such as high cost and limited availability for their widespread using. The study of markers of bone remodeling normally and in pathology helps to assess the quality of bone tissue indirectly, gives prospects in the selection of targeted therapy and improvement of early diagnosis of osteoporosis.

Key words: *osteoporosis, bone remodeling, bone turnover markers*

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BMP — bone morphogenic protein; DXA — dual energy X-ray absorptiometry; M-CSF – macrophage colony stimulating factor; CTX — C-terminal telopeptide of type I collagen; PINP – procollagen type I aminoterminal propeptide; OPG — osteoprotegerin; RANK — receptor activator of nuclear factor kappa-B; RANKL — RANK ligand; TRAP 5b — tartrate-resistant acid phosphatase 5b; BMU — basic multicellular unit

Introduction

Osteoporosis is a metabolic skeletal disease, which is characterized by its tendency to decrease bone mass and deteriorate the microarchitecture of bone tissue, leading to fragility fractures [1]. The number of patients with osteoporosis is steadily increasing due to the aging of society. Osteoporosis affects about 200 million people worldwide, and about 8.9 million fractures are fragility fractures [2]. In Russia, among the people aged 50 and older, osteoporosis is diagnosed in 34% of women and

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27% of men. The social significance of osteoporosis is evident in its consequences: fractures of bones of the peripheral skeleton and vertebral body fractures leading to high material costs and causing a high level of disability and mortality [3].

Bone strength is determined by the quantity and quality of bone tissue. Measuring bone mineral density (BMD) using dual energy X-ray absorptiometry (DXA) is the gold standard for studying bone tissue quantity. The bone quality is assessed by its microarchitectonics, presence of microdamage, the remodeling parameters, and the ability of bone tissue resist fracture [4]. Currently, the following different methods for assessment of the bone quality parameters are available: trabecular bone score [5], high-resolution peripheral quantitative computed tomography, high-resolution magnetic resonance tomography [6], microcomputer tomography, bone histomorphometry [7], bone microindentation testing [8]. However, these methods have limitations for their widespread use, such as high cost and limited availability.

Thus, the study of bone remodeling under normal and pathological conditions helps us to indirectly assess the quality of bone tissue, provide perspectives in the selection of targeted therapy, and improve early diagnosis of osteoporosis.

Normal Cycle of Bone Remodeling

Bone remodeling can be divided into 2 types: stochastic (probabilistic) and targeted. Targeted remodeling is activated when microdamages occur in bone tissue and osteocytes die [9]. Stochastic remodeling is regulated by a number of hormones (parathyroid hormone, estrogens, STH, and free T4) [10].

Cycle of Bone Remodeling

Osteocytes of intact bone produce the glycoprotein sclerostin which prevents differentiation of mesenchymal stem cells (progenitor cells) by blocking the Wnt/β-catenin signaling pathway. When microdamage occurs in bone tissue, the osteocytes transmit a mechanical signal (transduction) and a chemical signal (release of prostaglandins, growth factors, and nitric oxide) to the bone lining cells that line the surface of the bone trabecula. In response to incoming signals, the bone lining cells detach from the bone surface, forming so-called "canopy". Cells of the "canopy" are connected to the osteocyte network via gap junctions, to the lining cells on quiescent surfaces [11], and to a capillary, forming a bone remodeling compartment (BRC). BRC blood supply is provided by capillaries either coming from the marrow space (in cancellous bone) or from the central vessel of the Haversian system (in cortical bone) [12]. It is assumed that the osteocytes death as well as the release of osteotropic growth factors and cytokines stimulates angiogenesis. At the same time, the angiogenic factors VEGF (vascular endothelial growth factor) and endothelin regulate the activity of osteoclasts and osteoblasts [13], taking an active part in signaling between blood vessels and bone tissue [14]. Osteoprogenitor cells under the cover of bone lining cells become free from the sclerostin exposure and enter the process of differentiation into preosteoblasts under the influence of growth factors and interleukin-1. Some osteoblastogenesis markers are the transcription factors Runx2 (Runt-related transcription factor 2, and transcription factor 2, which is associated with dwarfism) and Osterix (Osx) [15].

Nearly all stages of osteoblastogenesis are associated with activation of the Wnt signal: differentiation of the mesenchymal stem cell into preosteoblast, as well as survival and continuation of differentiation of preosteoblasts into osteoblasts. Wnt-proteins activate the Wnt/β-catenin signaling pathway, triggering osteoblastogenesis processes. The Wnt/β-catenin signaling pathway consists mainly of Wnt ligands (or wingless-type MMTV integration site family ligands), Fz receptors (Frizzled), LRP5/6 coreceptors (a protein bound to a low-density lipoprotein receptor of types 5 and 6), Dsh protein (Disheveled), β-catenin, GSK-3β (glycogen synthase kinase-3β), Axin protein (axis inhibition protein 1), APC (adenomatous polyposis coli and suppressor protein), CK1 (casein kinase 1), and TCF/LEF (nuclear T-cell transcription factor / lymphoid enhancer factor) [16]. In the absence of the Wnt ligand, a multiprotein complex is formed in the cell cytoplasm, including APC, CK1, Axin, and GSK-3β. This complex facilitates GSK-3β-dependent phosphorylation of β-catenin and its subsequent ubiquitination, which leads to further degradation of β-catenin in the proteasome. Thus, β-catenin does not translocate into the cell nucleus and does not trigger the

osteoblastogenesis processes. Upon activation of the canonical Wnt/β-catenin signaling pathway (cWnt-SP), Wnt ligands bind to Fz (Frizzled) and LRP5/6 to form the Wnt-Fz-LRP5/6 ternary complex. This complex is stabilized by the proteins Dsh and Axin, resulting in the formation of "receptor complex" Wnt-Fz-LRP 5/6 -Dsh-Axin on the cell surface. This inhibits GSK-3β-phosphorylation of β-catenins, which leads to the cessation of their degradation. β-catenins penetrate the nucleus, and they interact with the transcription factors TCF/LEF, resulting in the activation of target genes (Figure 1).

These target genes include genes encoding non-collagen bone matrix proteins (osteocalcin, osteopontin, bone morphogenetic proteins (BMP)), type I collagen, SP7 gene (encodes transcription factor Osterix), and ALPL (determines alkaline phosphatase). Also, Wnt signaling stimulates osteoprotegerin (OPG) secretion [17].

There are 19 Wnt ligands that have been described in humans, and they can activate both canonical and non-canonical signaling pathways. These include Wnt1, Wnt2, Wnt2B, Wnt3, Wnt3A, Wnt4, Wnt5A, Wnt5B, Wnt6, Wnt7A, Wnt7B, Wnt8A, Wnt8B, Wnt9A, Wnt9B, Wnt10A, Wnt10B, Wnt11, and Wnt16 [18]. Sclerostin, DKK-1 (Dickkopf-related protein 1), and Wnt-inhibitory factor 1 (WIF-1) are the antagonists of the Wnt / β-catenin signaling pathway [19].

BMP-2 (bone morphogenetic protein 2) is able to stimulate angiogenesis, enhancing the secretion of the endothelium growth factor by osteoblasts.

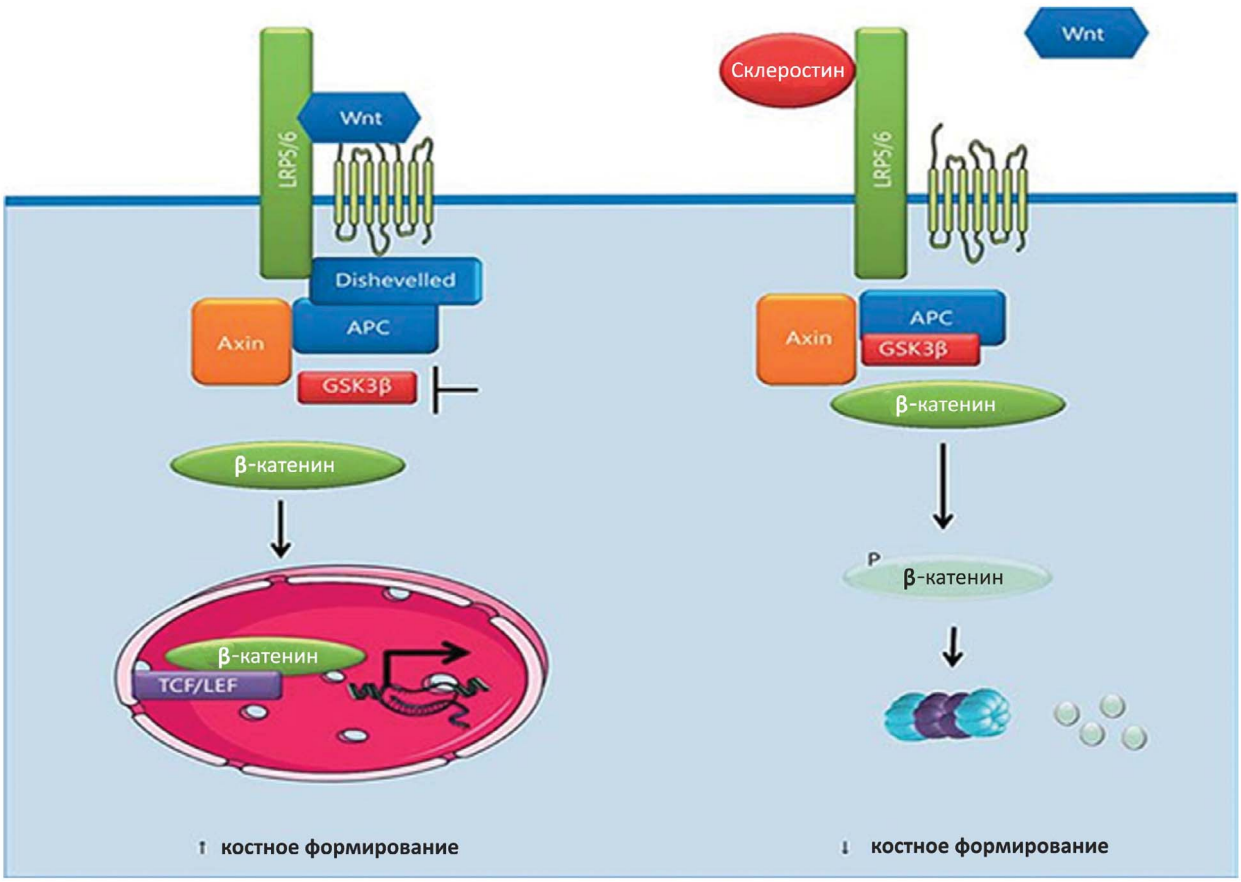

Figure 1. *Copyright © Gerontology 2016;62:618–623 DOI: 10.1159/000446278: Description of the canonical Wnt/β-catenin pathway and its regulation by sclerostin. Wnt binding to Frizzled and LRP5/6 coreceptor promotes the recruitment of Dishevelled that destabilizes the GSK3-Axin complex. Then, GSK3 inhibits the phosphorylation of β-catenin, leading to its intracellular accumulation and to its translocation into the nucleus. Thereafter, β-catenin forms a complex with T-cell factor/lymphoid enhancer factor (TCF/LEF) and promotes bone formation. In the absence of Wnt, the cytoplasmic complex containing GSK3 allows the phosphorylation of β-catenin and promotes its ubiquitination. Sclerostin induces an inhibition of the non-canonical pathway. By binding to LRP5/6, sclerostin prevents the association LRP5/6-Frizzled receptor and then inhibits bone formation. APC = Adenomatous polyposis coli.*

BMP-2 induces osteogenesis through enhanced activation of the Wnt / β-catenin signaling pathway. In addition, BMPs belonging to the superfamily of the transforming growth factor beta (TGF-β) proteins are responsible for numerous cellular regulatory processes, including osteogenesis and regulation of bone formation [20]. The BMP ligand binds to serotonin-threonine-kinase receptors of the 1st and 2nd types (BMPR) on the cell surface. Interaction with the receptors leads to activation of intracellular signal proteins Smad-1, -5 and -8 (9), which are transported to the nucleus and act as transcription factors, resulting in the activation of BMP-dependent genes [21, 22]. In particular, BMPR-IA and BMPR-IB are involved in the differentiation of mesenchymal stem cells [23]. BMP-2, BMP-4, BMP-7, BMP-9, and BMP-13 are usually studied in the context of osteoblastogenesis and bone formation [24, 25]. It is noteworthy that BMP-2 stimulates expression of Runx2 in osteoprogenitor cells and expression of Osx and the distal-less homeobox 5 gene (Dlx5 gene) in osteoblasts [26]. BMP-3 is an exception because it inhibits osteogenesis [27]. BMPs function as both autocrine and paracrine factors, and their synthesis is induced by the BMP themselves through local feedback mechanisms [28].

Preosteblasts also release a macrophage colony-stimulating factor (M-CSF), which interacts with its high affinity transmembrane receptor (c-fms) located on macrophage lineage cells in capillary circulation, which leads to their differentiation in preosteoclasts. Preosteoclasts express RANK (receptor activator of nuclear factor kappa-B), and preosteoblasts express RANKL. RANKL belongs to the of tumor necrosis factors family TNFSF11. RANK activation by RANKL binding induces the activation of transcription factors, such as c-fos, NFAT (nuclear factor of activated T cells) and nuclear factor kappa B (NF-kB) in preosteoclasts, which leads to its differentiation into mature osteoclast [29, 30]. M-CSF is a cofactor for RANKL/RANK, which mediates osteoclastogenesis. Experimental data showed that RANKL can stimulate bone resorption in mice which have no M-CSF [31]. Conversely, only M-CSF is not sufficient to activate osteoclasts. Therefore, RANKL plays a decisive role in osteoclastogenesis and is necessary for bone resorption [32].

Osteoclasts with αvβ3 integrins and bone matrix proteins (osteopontin, bone sialoprotein) are fixed on the bone surface and produce cathepsin K, cysteine protease, matrix metalloproteinases, and hydrogen ions [33]. Cathepsin K is a lysosomal cysteine proteinase, which is one of the enzymes which destroy type I collagen, the main component (90%) of bone matrix [34]. Cathepsin K is the main proteolytic enzyme of osteoclasts and, therefore, one of the most specific markers of bone resorption. Due to the action of cathepsin K, large fragments of collagen consisting of N-telopeptides and associated transverse pyridine cross-links (cyclic pyridinolines (PYD) and deoxypyridinolines (DPD)) enter the bloodstream from the bone resorption zone. Matrix metalloproteinases (MMPs) belong to a family of zinc- and calcium-dependent endopeptidases that impact the metabolism of the components of the extracellular matrix. If cathepsin K cleaves the N-terminal portion of the collagen (NTX, Amino-terminal cross-linked telopeptide of type 1 collagen), the MMP forms large fragments in the bone resorption zone, consisting of two C-telopeptides of the same type I collagen molecule (CTX, Carboxy-terminal cross-linked telopeptides of type I collagen), a spiral segment of another collagen molecule, and transverse pyridine cross-link between them. These fragments, which are designated as CTX-MMP, enter the bloodstream and are then excreted in the urine. However, their structure is unstable and destroyed by the action of cathepsin K as well as proteolytic enzymes in the vascular bed, resulting in circulation of various fragments of C-telopeptides in the bloodstream [35].

Due to the action of proteolytic enzymes and acidification, the Howship's lacuna is formed. Transcellular transport of microvesicles containing bone matrix degradation products into the cell is performed by means of tartrate-resistant acid phosphatase 5b (TRACP 5b). This enzyme is synthesized by osteoclasts. The activity of bone resorption processes can be measured by the level of TRACP 5b in blood plasma [36, 37].

IGF-1 (insulin-like growth factor-1), IGF-2, and TGF-β (transforming growth factor β) are released from the bone matrix during resorption [33].

Preosteoblasts, which are completely differentiated into the osteoblast, stop RANKL synthesis on the cell surface and start secreting OPG (osteoprotegerin).

OPG (TNFRSF11B) is a member of the TNF family, which is secreted not only by osteoblasts, but also by bone marrow stromal cells [38] and T cells [39]. OPG protects the skeleton from excessive bone resorption, acting as a soluble receptor, a decoy molecule that can bind to RANKL [40]. The binding of OPG with RANKL subsequently inhibits the binding of RANKL to its RANK receptor [38]. Overexpression of the gene encoding OPG leads to the development of high bone mass and a decrease in the number and activity of osteoclasts [41]. In physiological conditions, the OPG/RANKL ratio is in equilibrium and bone homeostasis is maintained. The OPG/RANKL ratio is an important factor for determining bone mass and skeletal integrity [42]. TNF-α, IL-1, IL-4, and IL-6 modulate the RANKL/RANK ratio by stimulating and enhancing RANKL expression on T cells. The cross-regulation between bone and immune cells is considered as a bone immunological niche [43].

Mature osteoblasts fill the resorption cavity, producing a variety of bone matrix proteins and type I collagen, resulting in organic matrix formation (osteoid) which later becomes mineralized. The osteoid predominantly consists of type I collagen, which is formed from type I procollagen synthesized by fibroblasts and osteoblasts. Procollagen type I has N-terminal and C-terminal propeptides (Procollagen type I C-terminal propeptide, PICP; Procollagen type I N-terminal propeptide, PINP) that are removed by specific proteases when procollagen is converted into collagen. The N-terminal propeptide of type I collagen is released into the intercellular space and the bloodstream when the type I collagen is formed and incorporated into the bone matrix, and it is one of the markers of bone formation [44].

Some osteoblasts extending deep into the osteoid are transformed into osteocytes. Other osteoblasts are differentiated into bone lining cells, and the rest (up to 80%) undergo apoptosis. The cells of a "canopy", which previously formed the tent cover of the resorption zone, return to their original position. Newly formed osteocytes restore the syncytium and begin to secrete sclerostin. As a result, all processes of cell differentiation are fully terminated [45].

Bone remodeling occurs in the basic multicellular unit (BMU), which is a microcavity with osteoclasts, osteoblasts and osteocytes. During normal bone remodeling, the resorbed bone is completely replaced by the new bone in the same amount and location [12]. Factors controlling these processes are molecules excreted by osteoclasts that induce bone formation at the BMU level either by attracting osteoprogenitor cells and osteoblasts or by stimulating their differentiation and activation.

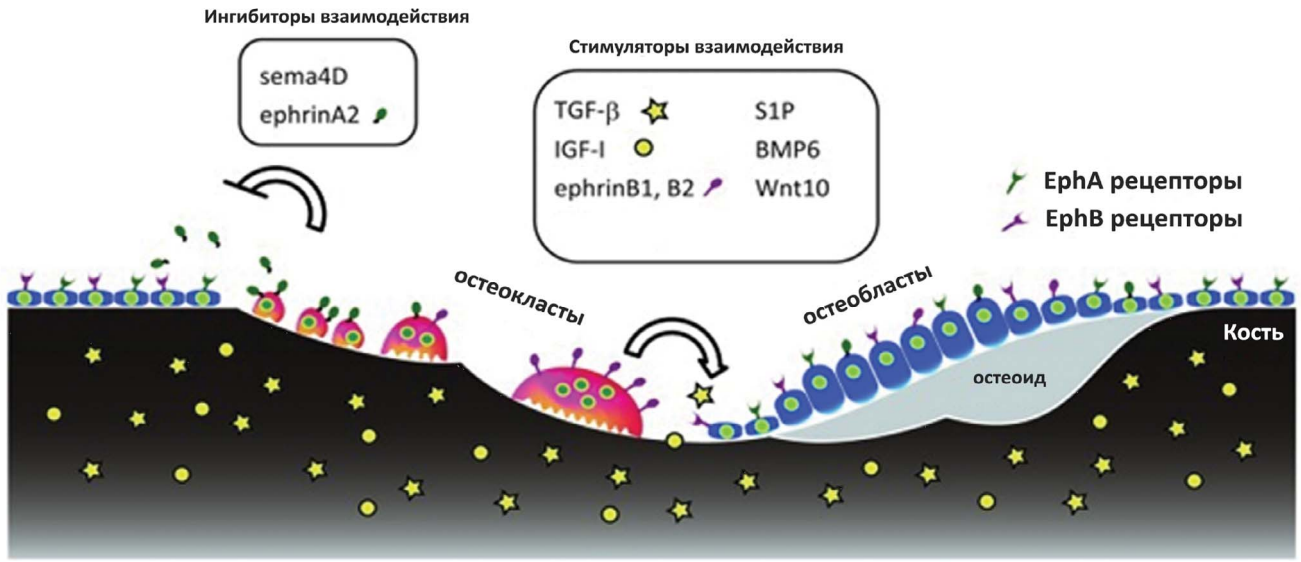

Figure 2. *Cell Adhesion & Migration 6:2, 148–156; March/April 2012; © 2012 Landes Bioscience: Coupling stimulators and inhibitors during bone remodeling. Bone matrix contains TGF-b (yellow stars) and IGF-I (yellow circles), which are released by osteoclastic bone resorption to stimulate coupling. Cells in the osteoclast lineage (red) produce various coupling stimulators and inhibitors that act on osteoblasts or their progenitors (blue).*

Transforming growth factor b (TGF-b) and insulin-like growth factor-1 (IGF-1) are released from the extracellular matrix during bone resorption, while factors such as cardiotrophin-1, sphingosine-1-phosphate, BMP6 and Wnt10b are secreted by osteoclasts [46]. EphrinB1 and ephrinB2 are located on the cell membrane and act only locally for the transition from a bone resorption to an osteogenesis phase in BMU [47].

Eph-receptors belong to the family of receptors-tyrosine kinases, which are activated by ephrin ligands. Both Ephs and ephrins are divided into two groups: A and B. As a rule, EphA receptors (EphA1–A8, A10) interact with ephrinA (ephrinA1–A5), and EphB receptors (EphB1–B6) interact with ephrinB ligands (ephrinB1–B3), with some exceptions [48]. As an exception, EphA4 binds to ephrinB2, ephrinB3, and ephrin As. Eph receptors interact with ephrin ligands on the cell surface, initiating bidirectional signaling: forward signaling through Eph-receptors, and reverse signaling through the ephrin ligand [49]. Bidirectional signaling between the osteoblasts ephrinB2 ligands and the osteoclasts EphB4 receptors inhibits osteoclastic bone resorption and increases osteoblastogenesis by transitioning between two states (Figure 2). Parathyroid hormone (PTH) induces ephrinB2 formation in osteoblasts and enhances bone formation. In contrast to ephrinB2, ephrinA2 acts as an inhibitor of bone formation [50].

Remodeling in cancellous bones lasts on average about 200 days, and resorption lasts for 30-40 days. The period of formation is about 150 days [51]. Remodeling of the cortical layer is faster and takes about 120 days [52].

Specific Aspects of Bone Remodeling in Primary Osteoporosis

Osteoporosis is a multifactorial disease, the development of which depends on lifestyle, genetic predisposition, concomitant diseases, physical activity, medication intake, endocrine status, human aging and individual longevity [53].

Genetic studies have shown that polymorphisms of Wnt10B impact the reduction in bone mass and the risk of osteoporosis [54]. Wnt10b seems to be a modulator of bone regeneration and homeostasis. β-catenin deficiency leads to the arrest of osteoblasts development at an early stage in mesenchymal osteoblastic precursors and impairs maturation and mineralization of osteoblasts [55].

There is evidence that mesenchymal stem cells in patients with osteoporosis have a function disorder, and this damage is associated with BMP signaling [56]. However, BMP antagonists have been described, including noggin (NOG) and gremlin (GREM). Overexpression of NOG, as shown in studies of transgenic mice, leads to a decrease in BMD due to increased inhibition of bone formation [57]. Single nucleotide polymorphisms in the NOG gene are associated with the phenotypes of patients with osteoporosis [58]. GREM is found in the skeleton, and its overexpression causes osteopenia and fractures [59]. Genetic variants of GREM2 are associated with bone mineral density (BMD), and GREM2 is considered a gene that increases the risk of osteoporosis [60].

Osteoporosis with an excessive number of osteoclasts is observed in patients with OPG deficiency [61]. RANKL is upregulated in conditions of osteoporosis, which is associated with downregulation of OPG [62]. In addition, the activity of some cytokines increases in patients with osteoporosis, including, in particular, TNF-α, IL-1, IL-4, and IL-6 [63]. The literature data showed that the malfunctioning of T cells subpopulations and their proinflammatory cytokines is associated with the development of osteoporosis. At the bone level, Th1 and Th2 cells affect the formation and activity of osteoclasts indirectly through secreted cytokines, including RANKL [64]. In addition, Th17-cells, a special line of proinflammatory T-helpers, have recently been identified as a potential T-cell subpopulation that plays a role in bone destruction [65]. The number of Th17 cells was found to be elevated in many bone diseases and in osteoporosis in particular. Th17 cells produce IL-17, which is able to mediate the differentiation of osteoclasts [66]. It is significant that Th17-helper cells also produce RANKL, which directly contributes to bone loss [65]. In addition, the Th17 population pool in the bone marrow and peripheral blood is found to be enlarged in postmenopausal osteoporosis [67]. Together, Th1/Th2/Th17 cells and their cytokines can play a key role as strong pro-osteoclastogenic mediators underlying the pathogenesis of osteoporosis (Figure 3).

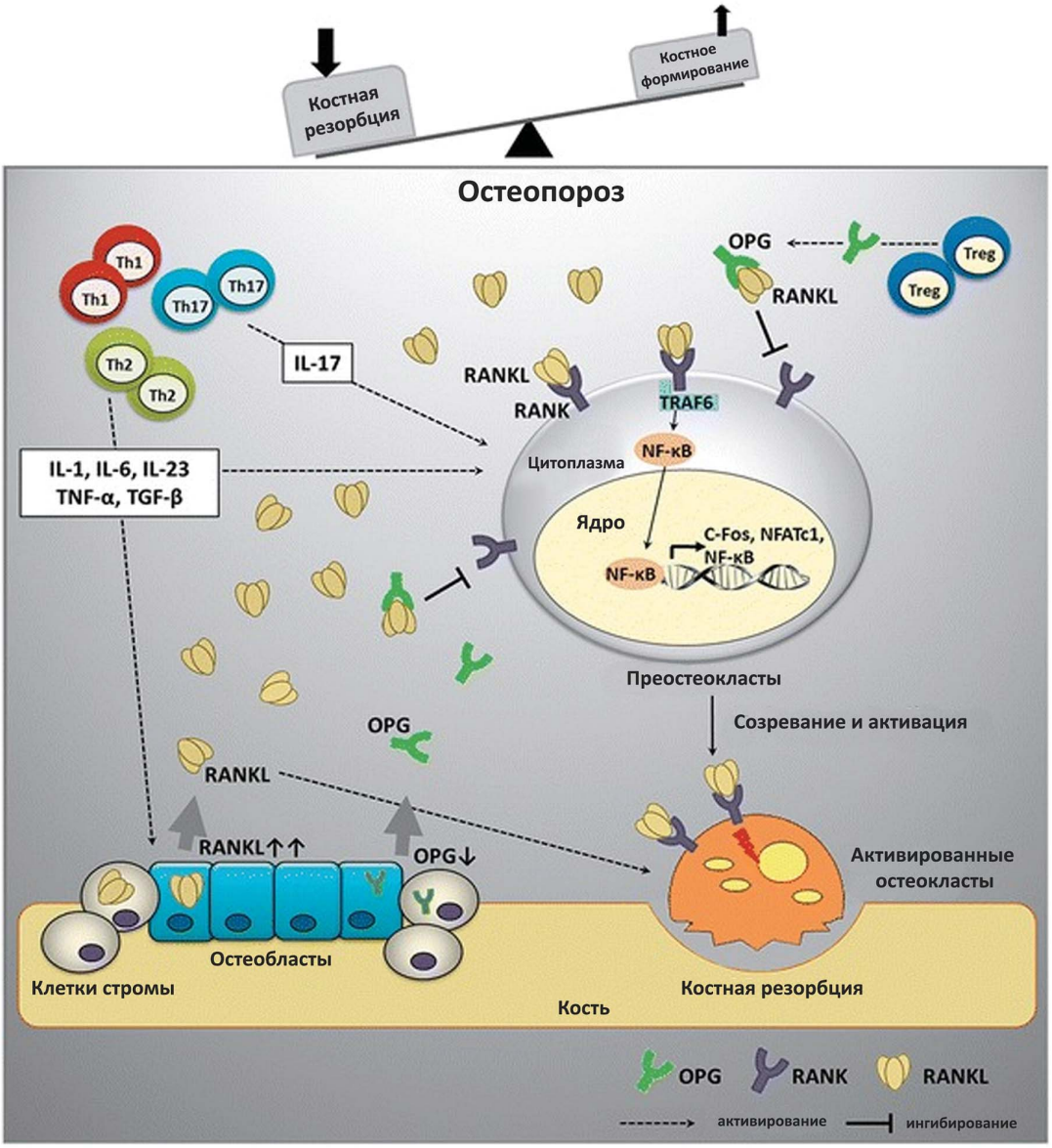

Figure 3. *©Copyright. Phetfong et al. Cellular & Molecular Biology Letters (2016) 21:12. Bone homeostasis regulation by OPG/RANK/RANKL system. RANKL which is secreted by activated T cells functions as an osteoclast-activating factor by binding to its receptor, RANK, which is expressed on preosteoclasts. RANKL-RANK binding induces the activation of several transcription factors in preosteoclasts and initiates several downstream signaling pathways that drive osteoclast differentiation and maturation. OPG which secreted by osteoblasts, bone marrow stromal cells, and T-cells acts as a soluble receptor that can bind to RANKL and subsequently prevents RANKL-RANK binding. Under physiologic conditions, OPG/RANKL is in equilibrium and preserves bone homeostasis. Under osteoporotic conditions, RANKL is upregulated, which is associated with downregulation of OPG. Several proinflammatory cytokines are secreted by T helper cells (Th1/Th2/Th17) stimulating and upregulating RANKL expression and mediating osteoclast formation and activity, which are linked to increased bone resorption.*

Bone Remodeling Markers

The bone turnover markers (BTMs) can be measured in blood or urine, and they reflect the metabolic activity of osteoblasts or osteoclasts, respectively. Bone remodeling markers are not specific to a particular disease.

Bone turnover markers include markers of bone formation, bone resorption, and bone metabolism regulators. Bone metabolism is studied by determination of enzymes, proteins, and by-products during the process of bone remodeling [68].

The markers of bone formation are osteoblast enzymes or by-products of active osteoblasts

produced during different phases of their development. Bone formation markers include total alkaline phosphatase (ALP), bone-specific alkaline phosphatase (BALP), osteocalcin (OC), procollagen type I N-terminal propeptide (PINP), and procollagen type I C-terminal propeptide (PICP). PINP has several functional advantages: it has a low intra-individual variability and is relatively stable in serum at room temperature, being the marker of choice. PINP is released as a trimeric structure, but it is rapidly broken down to monomeric form by thermal degradation.

Markers of bone resorption are hydroxyproline (HYP), hydroxylizine (HYL), deoxypyridinoline (DPD), pyridinoline (PYD), bone sialoprotein (BSP), osteopontin (OP), tartrate-resistant acid phosphatase 5b (TRAP 5b), C-terminal telopeptide of type I collagen (CTX or β-CrossLaps), aminoterminal telopeptide of type I collagen (NTX), and cathepsin K (CTSK). The majority of bone resorption markers are degradation products of bone collagen (HYP, HYL, DPD, PYD, CTX, NTX) and osteoclast-derived enzymes (TRAP 5b, CTSK). Early studies of bone metabolism were based on the determination of urinary DPD and PYD, which consisted in the collection of urine over a 24-hour period. That process was cumbersome and time consuming, leading to inaccuracies in their study. Plasma markers of bone resorption have now become available. It is more desirable to study them; CTX is the marker of choice.

The regulators of bone turnover are receptor activator of nuclear factor kappa-B ligand (RANKL), osteoprotegerin (OPG), dickkopf-1 (DDK-1) and sclerostin (SCL). DDK-1 and SCL are produced by osteocytes and inhibit the Wnt signal. Studies of the last decade have shown that osteocytes play a key role in regulating bone turnover due to the ability to detect changes in bone morphology, especially microcracks, due to mechanoreceptors. They regulate bone turnover through direct contact with other bone cells and through the production of different factors such as dickkopf-1 (DDK-1) and sclerostin (SCL), dentin matrix protein 1 (DMP1), and matrix extracellular phosphoglycoprotein (MEPE) [44] (Figure 4).

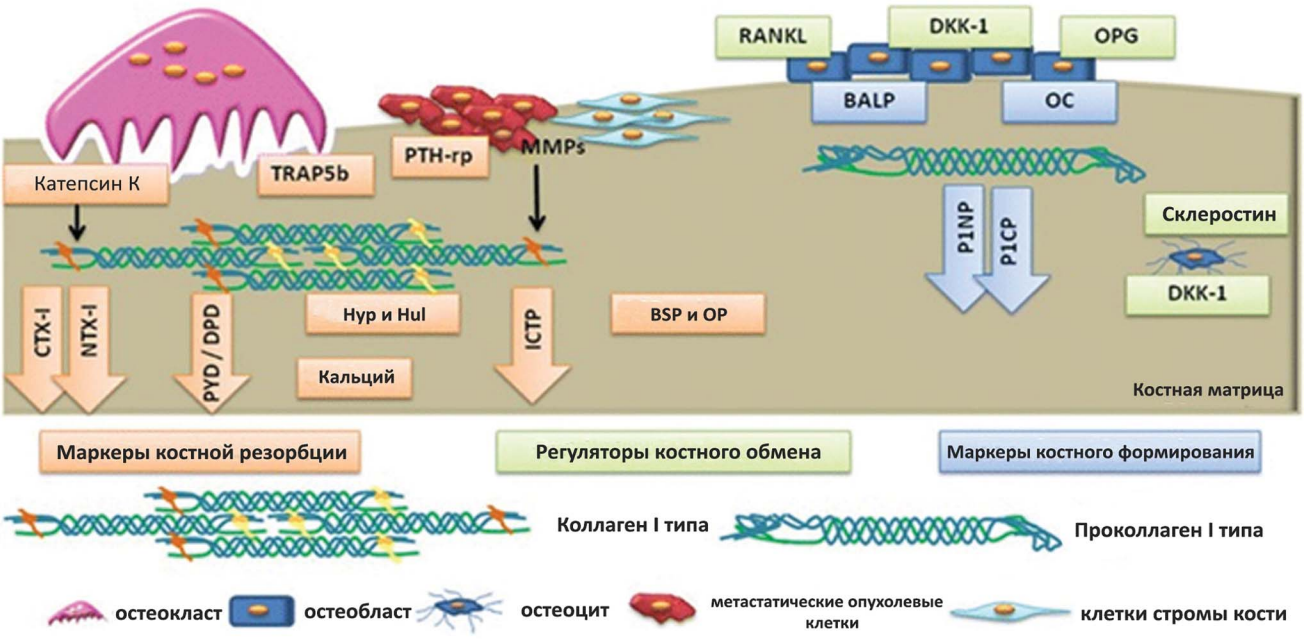

Figure 4. *Copyright © 2015, Nature Publishing Group. Biochemical biomarkers of bone turnover. Blue boxes/arrows represent bone formation markers: bone-specific alkaline phosphatase (BALP); osteocalcin (OC); propeptides of type I procollagen (P1NP and P1CP). Orange boxes/arrows represent bone resorption markers: pyridinoline (PYD); deoxypyridoline (DPD); C-terminal crosslinked telopeptide of type 1 collagen (CTX-1); N-terminal crosslinked telopeptide of type 1 collagen (NTX-1); hydroxyproline (HYP); hydroxylysine (HYL); bone sialoprotein (BSP); osteopontin (OP); tartrate-resistant acid phosphatase 5b (TRAP 5b); cathepsin K (CTSK). Green boxes represent regulators of bone turnover: receptor activator of NF kappa-B ligand (RANKL), osteoprotegerin (OPG), dickkopf-1 (DDK-1) and sclerostin.*

Over the last decade, significant advances have been made in identifying and evaluating specific bone turnover markers for use in clinical trials for medications and monitoring the therapeutic management of osteoporosis. The use of bone turnover markers is usually not recommended for selecting individuals at risk for fractures, partly due to their degree of variability. However, the analysis of the CTX resorption marker is recommended prior to the initiation of antiresorptive treatment, for example bisphosphonates or denosumab, and can be repeated at 3-6 months to check the effectiveness of the treatment and the patient's adherence to therapy. Similarly, a marker for bone formation, PINP, can be used to monitor anabolic treatment. The analysis of bone remodeling markers can also be useful in the monitoring process during drug "vacations" and for deciding when to resume therapy [69].

It is recommended to consider initiation of osteoporosis therapy in postmenopausal women with osteopenia at the level of bone remodeling markers in the upper quarter of the reference interval [3]. Therefore, the combination of a BMD examination using DXA and bone markers has great potential to improve the early diagnosis of individuals at high risk of developing osteoporosis.

Conclusion

The normal physiological process of bone remodeling involves a balance between bone resorption and bone formation. In osteoporosis, this process becomes unbalanced, resulting in gradual losses of bone mass and density due to enhanced bone resorption and/or inadequate bone formation. Several signaling pathways underlying primary osteoporosis have been identified, such as the osteoprotegerin/receptor activator of nuclear factor kappa-B (RANK) / RANK ligand (RANKL), bone morphogenetic proteins, and canonical Wnt-signaling pathway. Polymorphisms of Wnt10B, NOG gene, and GREM2 impact the reduction in bone mass and the risk of osteoporosis. The malfunctioning of T cells subpopulations and their proinflammatory cytokines is associated with the development of osteoporosis.

Currently, analysis of bone remodeling markers allows to study the function of osteoblasts, osteoclasts, osteocytes in health and in primary osteoporosis by noninvasive methods. It allows us to perform an early assessment of the effectiveness of anti-osteoporotic treatment that is conducted; identify individuals at high risk of osteoporosis in combination with the measurement of MBD; and determine the prospects for the selection of a targeted therapy in the future.

Conflict of interests

The authors declare no conflict of interests.

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