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TGF−β Signaling on Balancing Osteoblast, Osteoclast and Chondrocyte

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Abstract The balance of cartilage and bone cells (osteoblasts and osteocytes) plays a crucial role in cartilage homeostasis and bone remodeling. This review focuses on the TGF-β canonical signaling pathway, highlights its influence on cartilage homeostasis and bone remodeling and presents different inhibitor and clinical applications in bone diseases. This review aims at providing new ideas and directions for the prevention and treatment of bone diseases.

Key words TGF-β, bone remodeling, cartilage homeostasis, inhibitor, clinical application
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Transforming growth factor-β (TGF-β) is a member of a super-family of growth factors that regulate various cell growth, differentiation, and apoptosis[1]. It plays a role in modulating repair, inflammation, and immune homeostasis or tolerance[2]. Originally, TGF-β was discovered to be a factor that promoted anchorage-independent growth of fibroblasts[3]. More research showed that virtually every cell had the potential of producing TGF-β and responding to TGF-β, and that TGF-β could influence almost biological system tested *in vivo* and *in vitro*. The excellent comprehensive review of TGF-β activity is found in the literature[4]. TGF-β consists of five isoforms on separate chromosomes, but type 1 to 3 are only found in mammals. TGF-β1 is induced most rapidly in response to a variety of environmental stimuli[5]. TGF-β plays an essential role in tissue fibrosis in the kidney, liver, and lung, and can lead to immunological dysregulation. This review will focus especially on how TGF-β signaling pathways affect cartilage homeostasis and bone remodeling.

1 Structure and mechanisms of TGF−β

The TGF-β family consists of more than 30 members, including TGF-βs, bone morphogenetic protein (BMP), and growth and differentiation factor (GDF). TGF-β is a group of three different isoforms on separate chromosomes in mammals consisting of TGF-β1/2/3, which share a high level of homology over 80%[4]. Each of the three isoforms encodes a dimeric pro-protein (LAP)[6]. The latency-associated peptide (LAP), an 80-ku protein, is cleaved by the endopeptidase furin and remains noncovalently attached to TGF-β[7-8]. The LAP-TGF-β structure forms the small latent complex (SLC). The latent TGF-β binding protein (LTBP), a 125 to 160 ku protein, makes a disulfide link to LAP and is processed further to release active TGF-β[9]. The binding of LTBP to SLC forms a large latent complex (LLC) that regulates collagen and other tissue matrix proteins[10].

There are three different types of TGF-β receptors: TGF-β type I (TβRI), TGF-β type II (TβRII) and TGF-β type III (TβRIII). TβRII appears to be the core receptors, binding active TGF-β and recruiting the TβRI. The two pairs of TβRII and TβRI make up the activation complex for activating TGF-β, aided by TβRIII[11]. Within the engagement, TβRII phosphorylates the TβRI. While the TβRIII, which lacks kinase activity, is not associated with transmitting TGF-β signals, some reports show that increased expression of TβRIII is associated with enhanced TGF-β signaling, suggesting an essential role for TβRIII in TGF-β signaling. The soluble form of TβRIII inhibits the activation of TGF-β and prevents the binding of TβRI and TβRII[12].

The activated binding of TGF-β then signals through Smads, which is the canonical TGF-β

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signaling pathway. Eight mammalian members of the Smad family have been reported so far[13]. Smads are divided into R-Smads (receptor-regulated), Co-Smads (common mediator), and I-Smads (inhibitory) [14]. R-Smads composed of the N-terminal Mad homology (MH1) domain are phosphorylated by TβRI at C-terminal serine residues (MH2 domain). MH1 is conserved in R-Smads and Co-Smads. R-Smads directly phosphorylate, are activated by type 1 receptor kinases, and are anchored as dimers to the plasma membrane through SARA and other molecules[15]. Upon the activation of R-Smad, the interaction between MH1 and MH2 is disrupted, and R-Smads form hetero-oligomers with the Co-Smad *via* MH2 that translate the signal from the cytoplasm to the nucleus. I-Smads compete with R-Smads upon TGF-β stimulation and regulate the activation of TβRI by recruiting ubiquitin ligases to the activated TβRI[14]. Smad2 and Smad3 can be phosphorylated by the active receptor-like kinase 5 of TβRI[16]. The Co-Smad of mammals is Smad4[16], whose main function is to stabilize the structure of the Smad complex and assist its transfer to the nucleus of cells while maintaining effective transcriptional activity. Smad7, which has similar structure as R-Smads, can competitively bind TβRI[17]. It can prevent R-Smads from binding to type I and also recruit ubiquitin ligase to activate R-Smads to degenerate active type I receptors[18]. Smad7 interacts with transcription inhibitors in the nucleus and destroys function complexion of Smad-DNA induced by TGF-β[18]. As monomers in the cytoplasm, Smad exists in the absence of ligand stimulation. Once TGF-β binds, Smad2 and Smad3 are phosphorylated by TβRI and subsequently form a heteromeric complex with Smad4[19]. Smad6 inhibits the translocation of the complex of Smad2 and Smad4 by interfering with the phosphorylation of Smad2[20]. It has been reported that Smad5 can take part in inhibitory effects of TGF-β on human hematopoietic progenitor cells[21]. In addition, TGF-β activates the Smad-independent mitogen-activated protein kinase (MAPK) pathway, the extracellular signal-regulated kinase (ERK), p38MAPK, and the c-jun-N-terminal kinase (JNK). Signal transmission through these pathways may further regulate the Smad protein and mediate the Smad-independent TGF-β reaction. The signal conduction process of the TGF-β/Smads signal pathway is shown as Figure 1.

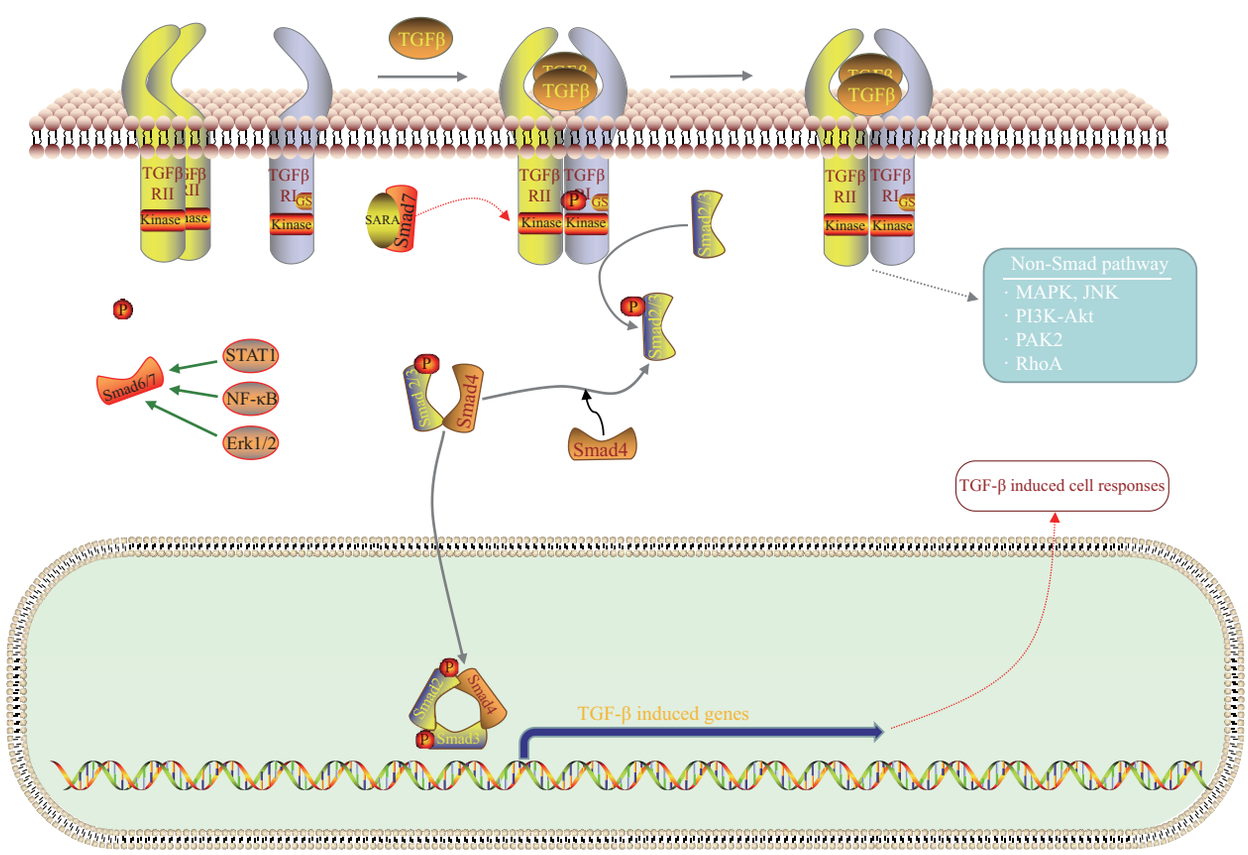

Fig. 1　TGF−β signaling pathways

2 Bone remodeling and cartilage homeostasis

Bone remodeling is the continuous process of bone resorption and bone formation. Bone remodeling can occur in multi-locations and at different times in order to replace the old bone and generate new bone. Bone is continuously being formed and resorbed to maintain the mineral homeostasis and structural integrity of the skeleton. Bone resorption and formation do not occur along the bone surface at random[19]. The bone remodeling process is accomplished through the precise coordination of the activities of two cell types: osteoblasts, which deposit the calcified bone matrix, and osteoclasts, which resorb bone[20]. The remodeling processes are governed by various growth factors and internal signals[21], which is also found in cartilage remodeling. The bone remodeling cycle is composed of six sequential phases: quiescence, activation, resorption, reversal, formation, and termination (Figure 2). The first phase involves the detection of signal in remodeling. There are mang conditions for remodeling, including mechanical strain and the secretion of Patrol Torpedo, Hydrofoil (PTH) [20]. These changes in mechanical strain initiate signals. PTH, the calciotropic hormone, is secreted by the parathyroid glands in response to reduced serum calcium. PTH combined receptors can activate protein kinase A and calcium intracellular signaling pathways. At the resorption phase, in response to PTH-induced bone remodeling, osteoblasts produce monocyte chemoattractant protein-1 (MCP-1) and enhance macrophage colony-stimulation factor (CSF-1) and RANKL[22]. These factors promote osteoclasts formation and activity. In the reversal phase, cells may receive or produce proteins that reverse the bone from resorption to formation in temporary anatomical structures[23]. During this formation phase, osteoclasts are replaced by osteoblasts. Many bone disorders are caused by an imbalance in this cycle.

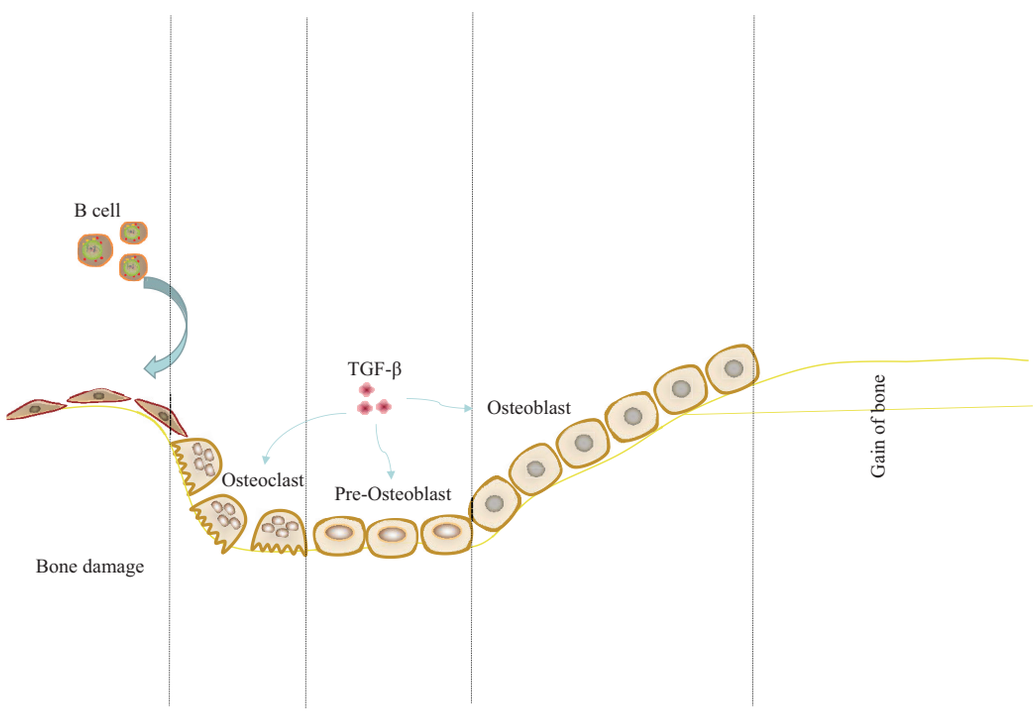

Fig. 2 Physiological bone remodeling

Cartilage homeostasis relies on the normal extracellular matrix structure, which is maintained by the balance between synthesis and degradation rates. Cell homeostasis requires defense mechanisms to protect cells from oxidants and prevent DNA mutations and telomere DNA damage. Articular cartilage, specifically the hyaline cartilage, covers the joint surfaces. Cartilage is composed of a specialized matrix of collagens, proteoglycans, and cellular components[24]. Chondrocytes are derived from

mesenchymal stem cells, which constitutes its unique cell type. Cartilage homeostasis is disrupted during aging and disease. In most studies, chondrocytes are essential for balancing cartilage homeostasis, which can be affected by mechanical injury, joint instability due to genetic factors, and biological stimuli[25]. TGF-β regulates chondrocyte metabolism, differentiation, and proliferation.

3 TGF−β in chondrocytes and cartilage biology

The continuously proliferating synovium and the formed blood vessels can infiltrate the articular cartilage surface and even destroy the articular cartilage by secreting a variety of cytokines and inflammatory mediators. After the articular cartilage is destroyed, the bone tissue is invaded by the fibrous tissue in the blood vessel, which continues to proliferate. Bone tissue inflammation and necrosis along with fibrous connective tissue proliferation and calcification eventually lead to joint deformity[24]. Some studies have shown that the removal of TGF-β in mouse articular cartilage and the interruption of TGF-β signal transmission will lead to loss of proteoglycan and cartilage degradation[25-26], indicating that TGF-β can stimulate chondrocyte proliferation and thus plays an important role in the formation and maintenance of cartilage.

Guo *et al*. [27] pointed out that TGF-β1 can promote the synthesis of a cartilage-specific matrix by inducing the differentiation of mesenchymal cells into chondrocytes, thereby protecting the cartilage matrix from being hydrolyzed and destroyed by various proteases. It can further enhance the self-regeneration ability of cartilage and assist in the reversal of cartilage damage. On the other hand, potential TGF-β1 activation in the bone microenvironment plays a very important role in regulating and controlling the bone rebuilding process[28]. Local injection of TGF-β1 in the joint cavity *in vitro* can significantly promote the synthesis of articular cartilage proteoglycan and promote the repair of articular cartilage, but the increase in local TGF-β1 expression also contributes to the formation of joint cavity fibrosis and affects joint function. Some research showed the mice could not form normal articular cartilage after the removal of TGF-β1, causing similar symptoms to arthritis. They also found that TGF-β1 can promote the synthesis and release of proteoglycan and collagen[29-30]. However, other studies have shown the opposite results. Itayem *et al*.[31] reported that TGF-β injected into the knee joint cavity of rats caused osteoarthritis. These controversial experimental results suggest that we should conduct more in-depth research on the role of TβR1 in arthritis and related signal pathways. In human chondrocytes cultured *in vitro*, both ALK1 and ALK5 are expressed. Studies have shown that in chondrocytes, the TGF-β1 signal promotes the synthesis of extracellular matrix proteins through ALK5, while the ALK1 pathway inhibits the synthesis of extracellular matrix proteins[32]. In other types of cells, the ALK1 pathway is related to the synthesis of extracellular matrix proteins[33]. The ALK5 pathway also shows mutual inhibition. Therefore, the imbalance between the ALK1 signaling pathway and the ALK5 signaling pathway may have an important relationship with the pathological process of arthritis. How cartilage affects the two pathways of TGF-β/Smad are not yet clear because of complex correlations between the various types of signals involved.

4 TGF−β and osteoblast

Osteoblasts are bone-forming cells that synthesize and secrete matrix proteins[34], which are different than bone marrow mesenchymal stem cells (BMSCs). With continued growth, osteoblasts undergo four stages in the process of bone formation: cell proliferation, extracellular matrix maturation, extracellular matrix mineralization, and osteoblast apoptosis, with various factors regulating these stages[35].

Osteoblasts are regulated by a variety of cytokines, with TGF-β being one of the key growth factors. TGF-β can not only regulate the proliferation and differentiation of osteoblasts through its effect on cell division and proliferation [36], but can also activate extracellular signal-related kinases, such as J-N N-terminal kinases and mitogen-activated proteins. Kinase p38 and other intracellular effectors induce the differentiation of mesenchymal stem cells into osteoblasts and promote the proliferation and differentiation of osteoblasts[37]. At the same time, they also synthesize an extracellular matrix that includes osteonectin and osteopontin fibronectin under the induction of osteoblasts and promotes matrix mineralization[38]. On the other hand, there are specific receptors for each subtype of TGF-β on the cell membrane of osteoblasts. TGF-β1 can bind to type I and type II receptors of osteoblasts[39-40] to form a phosphorylated functional complex and affect the level of cell transcription for corresponding regulation

through the Smad signal pathway.

It is reported that osteoblast and osteoclast can connect through cytokines and extracellular matrix interaction[41]. The connection between them is mediated by hemi-channels and gap junctions. The main component of gap junction is connexin, with connexin 43 (Cx43) mostly highly expressed. Liu *et al.*[42] believed that the expression of Cx43 was related to the Smad-dependent TGF-β. Smad2 or Smad3 connected with Smad4 can regulate the expression of Cx43 and is involved in bone cell activity. Okada *et al*.[43] found that puerarin promoted the formation of bone by stimulating the expression of Smad2/3 mRNA and the secretion of TGF-β. Moreover, TGF-β can induce self-expression of osteoblasts and expression of BMP-2, enhancing osteogenic capacity[44]. Dong *et al*. [45] demonstrated that orthosilicic acid could enhance the effects of osteoblast differentiation of rat BMSCs by BMP2/Smad1/5/Runx2 signaling pathway through the silicon-mediated induction of synthesis of Col-1 and osteocalcin. Zhang *et al*. [46] demonstrated that Cx43 and Smad1 promoted BMP induced differentiation of BMSCs into chondrocytes and inhibited osteoblast differentiation in Wistar rats.

5 TGF−β and osteoclast

Osteoclasts are a type of bone tissue component. They are multinucleated giant cells formed by hematopoietic stem cells under the action of M-CSF and interleukin (IL) [47]. The diameter of osteoclasts range from 20−100 μm and contain 2−20 nuclei. The cytoplasm is rich in organelles such as mitochondria, ribosomes, and Golgi apparatus, and has irregular shapes such as pseudopods and protrusions[48]. Osteoclasts are mainly distributed on the surface of the bone and around blood vessel channels in the bone. Its functional status can be divided into an exercise phase and reabsorption phase[49]. Cells can take different forms during different stages. The cells in the motility phase are flat and non-polarized cells, while the cells in the resorption phase are dome-shaped with protruding plate-like pseudopods.

The repair process of bone involves not only regeneration but also the removal of damage. This process consists of bone resorption, bone formation, and bone reconstruction at the defect, with bone resorption mainly completed by osteoclasts. The process of resorption goes through the following steps: osteoclasts attach to the surface of the bone in the defect, the cells are polarized, secreted substances initiate osteoclast action, the activated osteoclasts either leave the bone surface and transfer to a new bone surface for new bone resorption, or undergo apoptosis[50]. Once the osteoclasts leave the bone, the osteoblasts enter the bone surface to begin osteogenesis. In addition to bone resorption, osteoclasts also have a role in regulating osteoblast production[50].

TGF-β1 is abundant in the bone matrix[51] and is released and activated during osteoclast-mediated bone resorption[52]. Disruptions in TGF-β signaling, such as that seen in Marfan syndrome and Carmurati-Engelmann disease, alter bone structure and strength[53-54]. The release of matrix-bound TGF-β1 enhances the recruitment of osteoblast progenitors to sites of bone resorption[55]; however, TGF-β1 is insufficient for promoting osteoblast differentiation[56], and increased activation of TGF-β by osteoblasts delays osteoblast differentiation and mineralization[57]. Because of this, additional signals must be present near the resorbed area. Because osteoclasts are situated at the site of TGF-β release, TGF-β produces paracrine factors that promote the differentiation of osteoblast precursors and induce secretion of numerous factors, including Wnts, from osteoclasts that promote both the migration and differentiation of osteoblast precursors[58-59]. Weivoda *et al.*[49] showed that mature osteoclasts secrete Wnt1 to promote osteoblast differentiation. TGF-β stimulated osteoclasts are the source of these factors. Studies have showed that disruption of TGF-β in osteoclasts may contribute to the uncoupling of resorption and formation in aging bone[60]. The precise role of TGF-β1 in osteoclastogenesis remains unclear. Some research showed that TGF-β1 promotes osteoclast formation at low concentration (1−100 g/L), but prevents it at high concentration (0.1−10 μg/L)[61]. Zhao *et al.*[62] provided the first evidence that TGF-β1/Smad4 affects osteoclast differentiation by regulating miR155 expression.

6 TGF−β and bone remodeling

Bone remodeling is initiated by osteoclasts resorbing existing bone, followed by the recruitment of osteoblasts that secrete collagen and mineralized matrix proteins to replace resorbed bone[63]. Osteoclasts are affected by a variety of cytokines in the process of formation, proliferation, and differentiation[64]. TGF-β1 is released and activated during osteoclast-mediated bone resorption[65-66]. TGF-β1 activates Smad2/3 signaling through a

receptor complex consisting of TβR I and TβR II[67]. The disruption of TGF-β1 signaling can cause bone structure and strength alterations caused by Marfan syndrome and Camurati-Engelmann disease[68]. Weivoda *et al.* [49] reported that TGF-β1 induces secretion of numerous factors, including Wnts, from osteoclasts that promote both the migration and differentiation of osteoblast precursors. Osteoclasts produce factors that recruit osteoblasts and promote bone formation at bone resorption sites. Mature osteoblasts secrete BMP-6 and Wnt10b to promote osteoblast differentiation. TGF-β-stimulated osteoclasts have also been demonstrated to be the source of Wnt1[58]. TGF- β -mediated induction of TGF-β synthesis has been shown to occur at the transcription level *via* the AP-1 transcription complex[69]. This data shows that osteoclasts synthesize, secrete, and activate TGF- β. Osteoclast-mediated activation of latent TGF-β is likely to be an integral component for any involvement of TGF- β in the autocrine and paracrine regulation of coupling[70]. Anne *et al.* [71] investigated osteoclast survival in response to TGF-β and found that TGF- β inhibited apoptosis. TGF-β -mediated promotion of osteoclast survival is mediated by a novel TGF-β RI/RII, downstream TAK1/MEK/AKT/NF- κB, and Smad2/3 pathways. Induction of these pathways cause expression of pro-survival Bcl2 family members BclXL and Mcl-1 to block caspase-mediated osteoclast apoptosis. The regulation of TGF-β on osteoclasts requires further study, as results have still been controversial[71].

7 TGF−β and bone diseases

TGF-β is involved in human diseases due to the polymorphisms of TGF-β signaling, such as osteoporosis, multiple myeloma, and so on. Camurati-Engelmann disease (CED) is a genetic disorder that encodes the latency-associated peptide (LAP) of TGF-β1[72]. TGF-β1 can directly activate in CED. The aberrantly activated TGF-β1 in bone marrow disrupts the coupling between bone resorption and formation, which has been demonstrated to induce CED progression[73]. Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal-dominant disorder characterized by progressive extra bone formation in soft tissues (heterotopic ossification), such as skeletal muscle, tendons and ligaments[74-75]. The gene of FOP, ACVR1, encodes a type receptor of the TGF-β, ACVR1/ALK2, which transduces osteofenic signaling[76]. Myhre syndrome is bone disorder characterized of short structure, facial dysmorphism and bone anomalies. This disorder encodes Smad4 gene regulating TGF-β and extra-cellular matrix (ECM) homeostasis[77]. Aneurysms-osteoarthritis syndrome (AOS) is featured with aneurysma, dissections, skeletal and cutaneous anomalies. Some research showed that mutations in Smad3 contribute to AOS[78].

Bone disorder characterizations of osteoporosis include low bone mass and microarchitectural deterioration. The bone loss in postmenopausal women is mainly caused by an imbalance between bone resorption and formation. Estrogen increases TGF-β secretion by osteoblasts[79]. TGF-β induced RANKL expression, TGF-β, and estrogen can increase OPG. The ratio of RANKL and OPG prevent the recruitment of osteoclasts[80]. Osteogenesis imperfecta (OI) is caused by mutations in type I collagen genes. These changes can stimulate TGF- β signaling. However, the environment of OI results in excessive TGF-β activation, which contributes to low bone mass[81].

In bone tumors, TGF-β contributes to the growth of bone metastases. Multiple myeloma (MM) is characterized by the presence of an expanded monoclonal population of plasma cells secreting a monoclonal immunoglobulin in the bone marrow and the development of an osteolytic bone disease[82]. More and more TGF-β are observed in the bone matrix, stimulating IL-6 or RANKL which increases osteolysis and decreases bone formation. Blocking TGF-β signaling through a type I receptor inhibitor[83] can reduce tumor burden.

Osteoarthritis (OA) is characterized by subchondral bone remodeling, abnormal vascular proliferation, osteophyte formation, and synovial inflammation. Studies have shown that the TGF-β-Smad2/3 signaling pathway induces the expression of proteoglycan and type 2 collagen through activin-like kinase 5 (ALK5) receptors, both of which are derived from the extracellular matrix[84]. TGF- β can not only degrade the extracellular matrix and induce chondrocyte differentiation through the BMP/Smad1/5/8 signaling pathway, but also target genes such as Runx2 and Mmp13 downstream. These pathways can promote cartilage degeneration and induce the development of osteoarthritis[85]. At the same time, the TGF-β signaling pathway also has the potential to promote synovial fibrosis and osteophyte formation[86]. Some scholars have proved that the systematic use of TGF-β neutralizing antibodies targeting subchondral bone can inhibit the excessive

activation of TGF-β to prevent the degradation of joint soft bones, thereby preventing the development of OA[87].

8 Inhibitory factors of TGF-β signaling in bone

Inhibitory Smads (I-Smad, Smad6, Smad7) can impede TGF-signals in multiple ways. Smad6 overexpression blocks TGF-β signaling[88]. Upon being phosphorylated by TβR II, the activated TβR I recruits and phosphorylates Smad2/3 at the C-terminal. Activin membrane-bound inhibitor (BAMBI) has been reported as a general antagonist of TGF-β family members[89]. BAMBI can cooperate with Smad7 to inhibit TGF-signaling[89] and form a complex with Smad7 and TGF-β1 to inhibit the interaction between TGF-β1 and Smad3, which affects Smad3 activation. BAMBI can also form complexes with Smad7 and TβR I, which can impair the activation of Smad3[90]. Chondrocyte specific Smad6 transgenic mice show postnatal dwarfism, osteopenia, and delayed chondrocyte hypertrophy due to inhibited Smad1/5/8[91].

Ubiquitin-proteasomal degradation is related to TGF-β signaling. Smurf2, E3 ubiquitin ligase, target TGF-β, and Smad2/3 can cause ubiquitin-proteasomal degradation[92]. Ectopic overexpression of E3 in chondrogenic mesenchyme accelerates chondrogenic maturation and ossification. Smurf1 is also an E3 ubiquitin ligase. TGF-β upregulates Smurf1 synthesis *via* MAPK-ERK signaling. At the same time, SMURF1-specific siRNA attenuates the inhibitory effect of TGF-β on osteogenesis[93]. Arkadia is a RING domain containing E3 ubiquitin ligase, which has been previously shown to be a positive regulator of the TGF-β pathway. It has been shown to ubiquitylate and degrade Smad7, which causes an overall increase in TGF-β signaling[94].

It has been reported that microRNA plays an important role in skeleton homeostasis and TGF-β signaling pathways. Cuadra *et al.* [95] reported that eight miRNA are described in OA as follows: miR-29c, -93, -126, -184, -186, -195, -345, and -885-5p. These intracellular miRNA can also be found in extracellular form, which could be analyzed as possible biomarkers in later studies. MiR-146a increases in OA confirmed that Smad4 was a direct target. MiR-146a is involved in human chondrocyte apoptosis in response to mechanical injury and may contribute to the mechanical injury of chondrocytes, as well as to the pathogenesis of OA by increasing the levels of VEGF and damaging the TGF-β signaling pathway through the targeted inhibition of Smad4 in cartilage[96]. Whether through traditional regulators or miRNA, regulation of TGF-β signaling can play a role in new treatments for bone disease.

9 The clinic application of TGF-β inhibitor

Inhibition of TGF-β or its signal provides a therapeutic target for different diseases, including arthritis and cancer[97-99]. Some reports showed that it is possible to reduce signaling and use excessive TGF-β to neutralize or trap TGF-β ligand. These same studies found that receptor kinase inhibitors, such as the TβRI/ALK5 inhibitors, have several advantages. They act *via* ATP-competitive inhibition of kinase catalytic activity of TβRI/ALK5 upon its recruitment, causing phosphorylation and activation by TGF-β bond TβRIII[100-101]. The TGF-β kinase inhibitor SD-208 can prevent osteolytic breast progression. Recently, LY2109761 and LY2157299, inhibitors of TβR I/ALK5, have been reported in clinical trials concerning bone metastasis[102-103].

Genzyme developed a fully humanized TGF-β monoclonal neutralizing antibody, GC-1008, which was directed against three isoforms of TGF-β[104]. GC-1008 has completed phase I dose-escalation studies. PF-03446962, produced by Pfizer, is an antibody against AKL1[105]. This antibody has displayed obvious medical effects. Other studies indicated minimizing excessive levels of TGF-β can use ASO to reduce TGF-β synthesis and secretion. Antisense developed AP-12009, an ASO specific for the mRNA TGF-β2[106]. This is currently in early-phase clinical trials to generate ASO-modified tumor vaccines with the goal of reducing the immune inhibiting activity at the vaccine sites.

BMP can counteract TGF-induced EMT to stimulate the opposite process. Recently, pre-treatment, overexpression or systemic administration of BMP7 can inhibit the formation of bone metastases[107-108]. BMP7 may be used as a differentiation-inducing agent by countering TGF-β. Moreover, BMP7 is approved for clinical use in open fractures of long bone and spinal fusion[109].

There are effective treatment for patients with bone metastases is to combine treatment that antagonize the effect of TGF-β with other therapeutic. Buijs *et al.*[110] point that combined treatment of CD-208 and 2-methoxyestradiol improved survival more effectively and reduce osteolytic lesions than monotherapy.

10 Conclusion

The members of the TGF-βs are potent regulators of homeostasis and bone repair that act on cell proliferation, osteogenic differentiation, osteoclastogenesis, and osteoblast/osteoclast balance. A good knowledge of biological and characteristic signaling can help us develop uses for them. Aberrant transduction pathways can result in imbalance during bone remodeling and cause skeletal disease. So far, blocking TGF-β can provide promising therapeutic ways for bone disease treatment. Unfortunately, there still has not been success in clinical trials. Complete confirmation in bone remodeling is essential to facilitate the ongoing search for improved therapeutics for bone disease.

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TGF-β信号在成骨细胞、破骨细胞和软骨生理平衡的作用

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摘要　软骨和骨细胞（成骨细胞/骨细胞）之间的平衡在组织内稳态、骨重建及骨稳态中起着至关重要的作用。TGF-β超家族如TGF-βs调节骨的增殖、分化和功能。本文集中于TGF-β典型信号通路探讨，并重点介绍了其对骨重建及软骨稳态的影响，同时阐述了不同的抑制剂及其在骨疾病中的临床应用，旨在为骨病的防治提供新的思路和方向。

关键词　TGF-β，骨重建，软骨稳态，抑制剂，临床应用
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