IBMS BoneKEy. 2009 November;6(11):434-438
http://www.bonekey-ibms.org/cgi/content/full/ibmske;6/11/434
doi: 10.1138/20090409

COMMENTARIES

A Novel Role for TGF-β1 in Bone Remodeling

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Commentary on: Tang Y, Wu X, Lei W, Pang L, Wan C, Shi Z, Zhao L, Nagy TR, Peng X, Hu J, Feng X, Van Hul W, Wan M, Cao X. TGF-beta1-induced migration of bone mesenchymal stem cells couples bone resorption with formation. *Nat Med*. 2009 Jul;15(7):757-65.

Transforming growth factor-β (TGF-β) plays an important role in bone metabolism. In particular, TGF-β has been hypothesized to function as a coupling factor that links bone resorption to bone formation. However, the molecular mechanisms underlying the role of TGF-β during bone remodeling have yet to be elucidated. A recent study from Tang *et al*. now shows that TGF-β1 induced the migration of bone mesenchymal stem cells to the bone remodeling area (1). Moreover, the authors demonstrate that mice carrying a mutation in the *TGF-β1* gene develop Camurati-Engelmann disease (CED), a disease characterized by progressive diaphyseal dysplasia, and express high levels of TGF-β1 in the bone marrow, and they also show that TGF-β receptor inhibition partially rescues uncoupled bone remodeling (1). This work highlights a novel role for TGF-β1 in bone remodeling and suggests that TGF-β1 may serve as a potential therapeutic target for bone diseases.

Bone remodeling is an important biological and physiological event that determines both the quantity and quality of bone tissue and maintains homeostasis of serum calcium and phosphate (2). Bone remodeling processes include repetitive bone resorption by osteoclasts and bone formation by osteoblasts (2;3). Bone resorption and bone formation are closely associated with each other during bone remodeling events and the balance between bone resorption and bone formation is strictly controlled under normal physiological conditions. However, the development of inflammation, immune disease, endocrine disorders or tumors affects the balance of bone remodeling, and may subsequently lead to several bone diseases including osteoporosis, osteopetrosis or skeletal dysplasia.

It has been demonstrated that various cytokines and growth factors influence bone resorption and bone formation (3-5). Among the growth factors, TGF-β has been proposed to function as a potential coupling factor during bone remodeling (6). This conclusion has been based on the following findings: 1) TGF-β is abundantly present in bone tissues in a latent form that associates with latency-associated protein (LAP) (7); 2) The latent form of TGF-β appears to be eluted onto the bone surface and is activated by dissociation with LAP during bone resorption; and 3) TGF-β regulates bone formation by controlling both osteoblast differentiation and function (Fig. 1), a finding that is consistent with that of Tang and colleagues, who clearly demonstrate that the active form of TGF-β1 is released from bone during osteoclastic bone resorption (1). More interestingly, these authors also show that TGF-β1 recruited bone mesenchymal stem cells that are the precursors of osteoblasts to the bone remodeling area, and, as a consequence, coupled bone resorption with bone formation. Finally, the authors also indicate that Smad2 and Smad3, both of which are activated by TGF-β, are critical for the migration of bone marrow stem cells (1).

CED is an autosomal dominant disease that is characterized by bone remodeling disorders associated with hyperosteosis and

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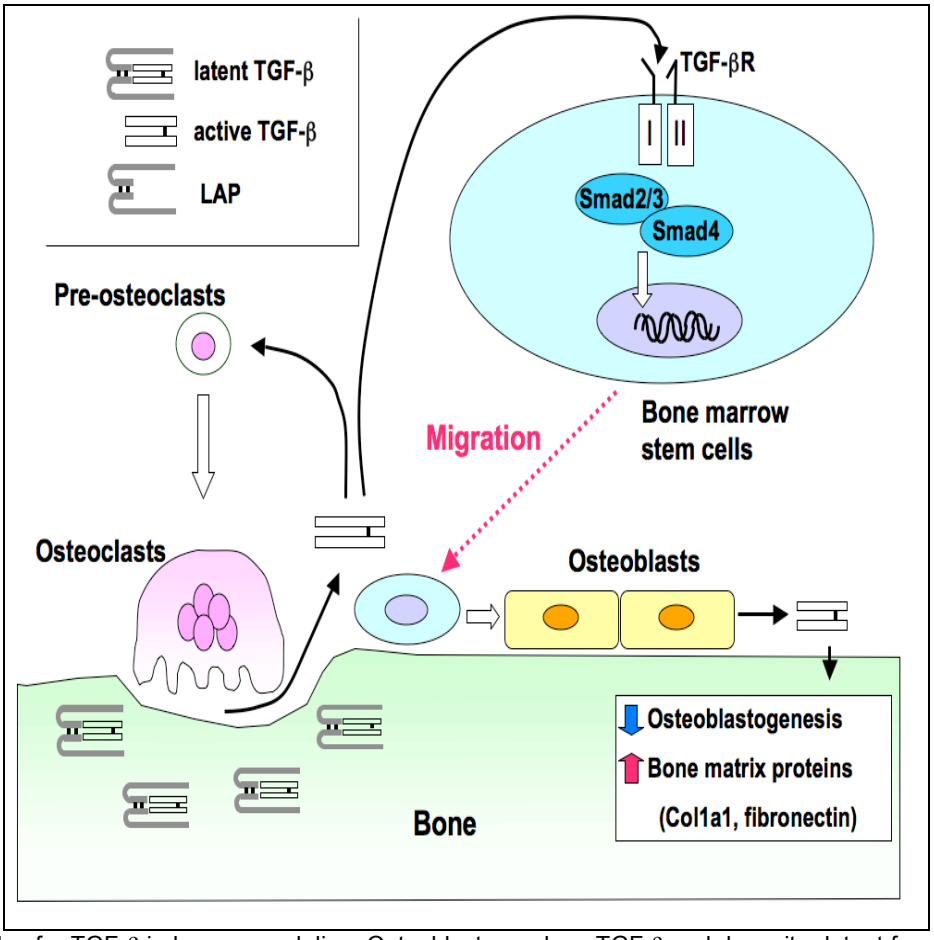

Fig. 1. Roles for TGF-β in bone remodeling. Osteoblasts produce TGF-β and deposit a latent form of TGF-β in bone tissue. During osteoclastic bone resorption, the active form of TGF-β is released from bone. The active form of TGF-β stimulates osteoclastogenesis and recruitment of bone marrow stem cells to the bone remodeling area. Although TGF-β increases the expression of bone matrix proteins, it also inhibits osteoblast differentiation of bone marrow stem cells.

sclerosis of the long bones and skull (8;9). The *TGFB1* gene that encodes TGF-β1 has been shown to be the gene responsible for the development of this inherited bone disease (8;9). Inhibition of the TGF-β receptor I (TβRI) is now shown to effectively rescue the CED phenotype in a mouse model (1). This finding suggests that TGF-β1 potentially represents an attractive therapeutic target for bone remodeling disorders. However, the effects of inhibition on CED mice are limited. The most likely reason for this observation is that TGF-β exhibits multifunctional activities. Transgenic mice over-expressing TGF-β2 develop osteoporosis in association with increased osteoclastic bone resorption (10). In addition, TGF-β has been shown to stimulate the osteoclastogenic action of receptor activator of NF-κB ligand (RANKL) (11). On the other hand, overexpression of a dominant-negative TGF-β type II receptor in the T cell lineage led to increased bone resorption in mice (12). Furthermore, a recent study indicates that TGF-β1 stimulates apoptosis of osteoclasts (13). Consequently, the precise role of TGF-β in osteoclasts and bone resorption appears to be quite complex.

The roles of TGF-β during osteoblast function and bone formation are also complicated. Bone morphogenetic proteins (BMPs) that belong to the TGF-β superfamily strongly stimulate osteoblastogenesis and subsequently

promote bone formation (14). BMPs exhibit strong osteogenic activity through activation of Smad1, Smad5 and Smad8 (15). Such BMP-regulated Smad signaling is critical for the normal regulation of expression and function of Runx2 and Osterix, essential transcription factors required for osteoblastogenesis and bone formation (14). In contrast, TGF-β exhibits bi-directional effects on osteoblast activity. TGF-β has been shown to stimulate expression of bone matrix proteins including type I collagen and fibronectin by osteoblasts (16;17) (Fig. 1). However, TGF-β is also known to markedly inhibit osteoblast differentiation, especially during the early stages of bone mesenchymal stem cell commitment to the osteoblast lineage (18). The molecular basis underlying TGF-β suppression of osteoblast differentiation has been reported previously (18). TGF-β was shown to activate Smad2 and Smad3 via TβRI, and activated Smad3 was found to physically interact with Runx2, an association that inhibits its transcriptional activity and osteogenic action via physical contact with the class IIa histone deacetylases 4 and 5 (18). In regard to osteoblast differentiation, TGF-β and BMPs appear to have opposite roles due to their utilization of distinct Smad molecules. Based on the study by Tang and colleagues (1), it can be suggested that TGF-β signals are downregulated after the recruitment by TGF-β of mesenchymal bone stem cells into the bone remodeling area. It is also possible that small amounts of TGF-β regulate the levels of bone formation stimulated by BMPs. Thus, future studies are required to clarify the mechanism governing the spatial and temporal regulation of TGF-β activity in the bone remodeling area. Such a dissection may provide a more precise understanding of osteoclast development and osteoblast differentiation during bone remodeling events.

TGF-β released from bone tissue also plays an important role in the metastasis of cancer to bone and in bone destruction by inducing parathyroid hormone-related protein (PTHrP) expression in cancer cells (19;20). Subsequently, PTHrP stimulates osteoclastic bone resorption through RANKL induction in osteoblasts, an event that results in the further release of TGF-β from bone tissues. Thus, TGF-β forms a vicious loop for the bone metastases of malignant cells. It may also prove very interesting to investigate whether TGF-β promotes the migration of cancer cells to bone metastatic sites. If this were to be the case, inhibition of TGF-β signaling might be used successfully in the future to treat bone metastases of various cancers.

Although this important study from Tang *et al*. (1) provides further evidence that TGF-β plays a critical role in bone metabolism, a few important points remain to be investigated. First, it remains unknown whether TGF-β2 exhibits activity similar to that of TGF-β1 in bone marrow stem cells, and second, whether the role of TGF-β in osteoblast differentiation may be investigated more appropriately using *in vivo* systems. How TGF-β inhibitors and stimulators are delivered specifically and efficiently to target cells is also a key issue that requires further investigation. The solutions to these issues may shed a great deal of light on the potential clinical applications of TGF-β in the treatment of bone disease.

Conflict of Interest: None reported.

Peer Review: This article has been peer-reviewed.

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