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News on current events in osteoporosis and rheumatology

TGF-β1 couples bone resorption with formation through migration of bone mesenchymal stem cells?

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Bone remodeling depends on the precise coordination of bone resorption and subsequent bone formation. Coupling of bone resorption and formation is believed to occur through the release, during osteoclastic bone resorption, of factors that have been trapped in the bone matrix during its formation. These factors direct the migration of bone mesenchymal stem cells to the bone resorptive surface, where they differentiate into osteoblasts. TGF-β1, one of the most abundant cytokine in bone matrix, is synthesized as a large precursor molecule, which is cleaved into active TGF-β1 and latency-associated protein (LAP) which remains linked to TGF-β1 as it deposits in bone. This complex, called latent TGF-β1, cannot activate its receptor and has to be dissociated to release active TGF-β1. TGF-β1 gene is mutated in Camurati-Engelmann disease (CED), a rare form of skeletal disease characterized by a progressive diaphyseal dysplasia, but all the mutations have been mapped to LAP and none of them altered TGF-β1 secretion or activity in vitro. Thus, the precise role TGF-β1 in bone remodeling remained unclear.

The study by Tang et al. [1] represents an important step in our understanding of TGF-β1 function in bone remodeling. The authors first demonstrated in vitro that bone resorption allows the conversion of latent TGF-β1 to active TGF-β1 and its subsequent release. Using both bone from TGF-β1 null mice and neutralizing antibody they further demonstrated that TGF-β1 is the main cytokine released form resorpting bone driving bone mesenchymal stem cell migration. Accordingly, TGF-β1 null mice showed reduced bone mass and reduced osteoblast recruitment to bone remodelling surface. TGF-β1 mutations from CED patients resulted, in vitro, in an impairment of LAP binding to TGF-β1 leading to the spontaneous release of active TGF-β1. The authors generated mice expressing either wild type or mutated TGF-β1 specifically in osteoblasts. These mice recapitulated the hallmark bone lesions of the human disease. Pharmacological inhibition of TGF-β1 signalling restored osteoblasts recruitment to the site of bone remodeling.

This study demonstrates that TGF-β1 functions to couple bone resorption and formation and suggests that a modulation of TGF-β1 activity could represents an effective treatment for bone remodeling diseases.

1. Tang, Y et al. *Nat Med* 2009; 15: 757-65

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TGF-β1, one of the most abundant cytokines in bone matrix, is synthesized as a large precursor molecule, which is cleaved into active TGF-β1 and latency-associated protein (LAP). The latter remains linked to TGF-β1 as it deposits in bone. This complex is called latent TGF-β1 and cannot activate its receptor. Bone resorption by osteoclasts allows the release of active TGF-β1 from LAP. Active TGF-β1 released at the site of bone resorption drives the recruitment of osteoblast precursors, enabling the coupling of bone formation to bone resorption.