

Contextual regulation of bone development, remodeling and regeneration by thrombospondin matricellular proteins

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Matricellular proteins – which include, but are not limited to, osteopontin, bone sialoprotein, tenascin C, SPARC (osteonectin), and thrombospondin family proteins - are components of the extracellular matrix which are highly expressed in the developing and mature skeleton. Members of this protein class serve as biological mediators of cell function by interacting directly with cells or by modulating the activity of growth factors, proteases, and other extracellular matrix (ECM) proteins. Although skeletons of matricellular protein-null mice are grossly normal, they each display unique deficiencies that are often magnified under pathological conditions. In addition, bone cells from wild-type and matricellular protein-null mice behave differently in various *in vitro* models of bone matrix synthesis and turnover. Because the biological effects of matricellular proteins are largely context dependent, *in vivo* and *in vitro* results must be considered together in order to fully appreciate the specific contributions that matricellular proteins make to bone physiology and pathophysiology. In particular, it is clear that although matricellular proteins are not required for bone development and function, the proteins act to modulate post-natal bone structure in response to aging, ovariectomy, mechanical loading, and bone regeneration.

Our laboratory specifically focuses on the role of thrombospondins in bone biology. We have examined bone formation and function in TSP2-null mice extensively, and have recently begun to characterize bone development in TSP1 and TSP3 mice. TSPs are multimeric, multi-domain proteins expressed ubiquitously in cartilage and bone. We have shown that TSP2-null mice have an increase in endosteal bone for-

mation, but that there are no apparent structural abnormalities in mature cortical bone or in growth cartilage. Examining the significance of an absence of TSP2 on the function of adult bones under varying pathophysiological stimuli has revealed other intriguing findings. TSP2-null mice show a lack of periosteal response but enhanced endocortical bone formation with *in vivo* loading of the tibia; they maintain bone mass in the absence of estrogen; and have enhanced fracture healing.

We believe that the cellular basis for these findings in the TSP2-null mice is that they have an increase in the number of marrow-derived mesenchymal stem cells (MSC). MSC are sequestered in the marrow and proliferate and differentiate to become endosteal osteoblasts. MSC exist in an ECM compartment composed primarily of loose collagen fibrils and non-collagenous ECM proteins, including TSP2. Thus, in the absence of TSP2 during loading, ovariectomy, or fracture healing, more osteoblasts are generated in the endocortical compartment.

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