

JMNI Special Issue: Basic Science and Mechanisms of Muscle-Bone Interactions

M. Hamrick

Medical College of Georgia, Augusta, GA, USA

A close functional relationship between muscle and bone is observed throughout growth, development, and aging, and this close relationship has provided a foundation for highly influential models of bone adaptation presented by such authors as D'Arcy Thompson, Julius Wolff, Melvin Moss, and Harold Frost. New technologies and experimental approaches now allow scientists to explore the muscle-bone relationship in even greater detail, which has facilitated the discovery of novel mechanisms and pathways at the tissue, cellular, and molecular levels that link muscle and bone anabolism and catabolism. This volume seeks to review some of the recent work in this area, and in so doing highlight new directions and therapeutic strategies for enhancing muscle and bone structure and function.

Muscle has long been recognized as a primary source of anabolic mechanical stimuli for bone tissue, yet the precise nature of the stimuli that induce bone formation (e.g., strain magnitude and frequency) has often been debated. The paper by Judex et al. reviews evidence that high-frequency, low magnitude stimuli are likely to favor the osteogenic differentiation of mesenchymal stem cells in bone. They present impressive data from a one-year interventional study in young women demonstrating the therapeutic potential of such stimuli for improving bone and muscle mass. Likewise, Qin et al. describe changes in intramedullary pressure with muscle stimulation that alter blood and fluid flow in bone tissue and induce bone formation. Again, these osteogenic stimuli are induced with relatively low magnitude, high frequency signals. The material reviewed by Judex, Qin, and colleagues underscores the point that while muscle is an important source of anabolic signals for bone, the signals do not necessarily need to be of the magnitudes we typically associate with forceful contraction en-

countered during high-impact or resistance-type exercise. Gross and colleagues investigate the other arm of the muscle-bone relationship, namely the effects of muscle disuse on bone catabolism. Using a Botox model to induce muscle paralysis, they show that rapid degradation of bone occurs in the presence of focal muscle paralysis. They suggest that "focally lost neuronal connectivity" is likely to play a key role in the bone loss that occurs with disuse or muscle paralysis. Thomopoulos and colleagues use a similar model to study alterations in the shoulder muscle-tendon-bone complex with muscle paralysis, and also find enhanced resorptive activity in bone with muscle damage. Together, these papers indicate that even very minor, localized muscular deficits can have dramatic effects on bone resorption. Future studies utilizing these innovative approaches will reveal specific molecular and cellular pathways linking muscle injury and focal bone loss.

The paper by Ravosa and colleagues uses a dietary intervention in rabbits to study muscle fiber type plasticity and corresponding alterations in the craniofacial skeleton. They find a marked increase in type II (fast-twitch) fibers with a hard diet, and this is associated with increases in bony dimensions of the mandible as well as with mineralization changes detectable using microCT. These findings are consistent with data from Elkasrawy, who shows increased bone mineral density throughout the skeleton of myostatin-deficient mice, mice that are also known to show a marked increase in the size and number of type II fibers. Interestingly, targeted increase of type II muscle fibers in adult mice was recently shown to reduce body fat and improve symptoms of metabolic syndrome induced by a high-fat diet¹, revealing the importance of muscle fiber composition to overall endocrine function. Hamrick and colleagues use *in vitro* and *in vivo* approaches to show that muscle is a local source of osteogenic growth factors (myokines), and Liu et al provide a review of evidence suggesting muscle-derived cells contribute directly to bone healing. Importantly, Liu and colleagues have recently used a novel mouse model to trace the migration of muscle-derived cells into the fracture callus², providing additional support for their model. These papers suggest that muscle is a local paracrine and endocrine source of secreted osteogenic factors, and is also a nearby reserve of potential os-

The author has no conflict of interest.

Corresponding author: Mark W. Hamrick, Ph.D., Department of Cellular Biology & Anatomy, Institute of Molecular Medicine and Genetics, Department of Orthopaedic Surgery, Medical College of Georgia, Augusta, GA 30912, USA
E-mail: mhamrick@mcg.edu

Accepted 2 February 2010

teoprogenitor cells. Thus, in addition to serving as a source of mechanical stimuli for bone, muscle also appears to be an important endocrine organ that may indirectly regulate bone metabolism through endocrine and/or paracrine pathways³⁻⁵ and provide progenitor cells that can be mobilized for bone repair when necessary. Perhaps the next question is how does bone “talk back” to muscle? That is, if muscle is a source of secreted factors and progenitor cells, how might bone-derived signals alter muscle metabolism, the migration of muscle-derived progenitors, or the secretion of various myokines?

There are several major themes that emerge from this volume. First, while the field of fat-bone interactions has provided a wealth of evidence linking fat-derived cytokines such as leptin, adiponectin, and IL-6 to bone metabolism, and adipose-derived stem cells are now seeing wider use in the clinic, the field of myokines and muscle-derived stem cells is not as far along. A more muscle-centric approach focusing on the regulation and secretion of myokines, the role of bone-derived signals in muscle physiology, and the factors mediating the migration and proliferation of muscle-derived stem cells to bone will shed new light on muscle-bone interactions. Second, animal models continue to provide key pieces of evidence on the mechanisms underlying muscle-bone interactions, and new mouse models¹ permit age- and tissue-specific alterations of gene expression in muscle tissue. Analyses of bone growth, aging, and repair utilizing such systems will allow for *in vivo* tests of mechanistic hypotheses linking neuromuscular function with bone modeling and remodeling activities. Finally, while current therapeutic strategies for preventing bone loss use small- and large-molecules to selectively target osteoblasts and osteoclasts, future therapies should also be directed at targeting muscle, particularly type II (fast-twitch) fibers. Muscle-derived changes in in-

tramedullary pressure, muscle-derived growth factors, and muscle-derived stem cells are all likely to contribute to bone formation and bone repair. Hence, molecular therapies that can maintain and improve neuromuscular function, and biophysical approaches (e.g., low magnitude, high frequency vibration) that can replicate muscle-derived anabolic stimuli for bone, may improve quality of life and reduce fracture risk in the elderly and in those with neuromuscular diseases. Indeed, by exploiting modern tools in molecular and cellular biology while at the same time appreciating the integrative nature of muscle and bone cross-talk we will ensure that the most exciting discoveries in musculoskeletal and neuronal interactions are yet to come.

References

1. Izumiya Y, Hopkins T, Morris C, Sato K, Zeng L, Viereck J, Hamilton JA, Ouchi N, LeBrasseur NK, Walsh K. Fast/glycolytic muscle reduces fat mass and improves metabolic parameters in obese mice. *Cell Metab* 2008;7:159-72.
2. Liu R, Peacock L, Schindeler A, Little DG. Myogenic progenitors contribute to ectopic bone formation in open fracture repair. *J Bone Miner Res* 2009;24(Suppl.1):SA0228.
3. Kaufman H, Reznick A, Stein H, Barak M, Maor G. The biological basis of the bone-muscle inter-relationship in the algorithm of fracture healing. *Orthopedics* 2008;31:751.
4. Pedersen B. Muscle as an endocrine organ: IL-6 and other myokines. *J Appl Physiol* 2009;107:1006-14.
5. Walsh K. Adipokines, myokines, and cardiovascular disease. *Circ J* 2009;73:13-8.