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MEETING REPORT

Bone–muscle interactions: ASBMR Topical Meeting, July 2012

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Meeting Report from the ASBMR Topical Meeting, Kansas City, MO, USA, 17–18 July 2012.

Introduction

In addition to its annual meetings, the American Society for Bone and Mineral Research (ASBMR) holds in a regular fashion 'topical meetings' to promote a more comprehensive and detailed discussion of a particular scientific topic of emerging importance. ASBMR members and others met in Kansas City, Missouri on 17–18 July 2012, for an exchange of ideas and research results on 'Bone and Skeletal Muscle Interactions'. New to this year's topical meeting was the inclusion of a pre-meeting workshop that allowed participants to spend a day learning selected research methodology employed in bone and muscle research. Workshop participants were guided through a series of hands-on training modules by researchers from the University of Missouri-Kansas City Center for Excellence in Dental and Musculoskeletal Research, the Muscle Biology Research Group, and the University of Missouri–Columbia. Another distinctive aspect underscoring the significance of this meeting was the presence of nine Program Officers/Directors of the National Institutes of Health (NIH). Some highlights of the meeting include:

Bone and Muscle Interactions during Development

In this session, different aspects of bone and muscle development were discussed including how development of the musculoskeletal unit (bone–tendon–muscle, BTM) is highly synchronized and tightly regulated. This interrelationship is demonstrated, for example, by the importance of muscle contractions for bone development,[1] and by the scleraxis regulation of bone morphogenic protein (BMP)-4 at the tendon–bone interface.[2] Although the biophysical and embryological aspects of the BTM unit during development are relatively well delineated, the biochemical interactions amongst the tissues and cells of the BTM remain mostly unknown.

Aging: Changes in Muscle and Bone, Linkages and Shared Etiologies

In this session, some of the lessons learned from developing and refining the clinical definition of osteoporosis were discussed and offered as a guide for developing an appropriate clinical definition of sarcopenia. For example, while bone mineral density provided a useful metric for defining an osteoporotic individual, the inclusion of measures of bone quality that better predict fracture risk can better identify individuals in need of and likely to benefit from clinical interventions. Likewise, the criteria used to define sarcopenia should take into account factors such as loss of mobility beyond a threshold,[3] which places individuals at risk for negative outcomes associated with sarcopenia, in addition to traditional measures of muscle mass and strength. The rather clear disconnect between muscle mass and muscle function should be carefully considered in the development of a sarcopenia definition, its prevention and treatment.[4] For example, weight training in the elderly can increase muscle strength by 174% at the same time that muscle mass only goes up 92%.[5] One conclusion is that there is a need for sarcopenia markers that can measure beyond loss of muscle mass, and probably a combination of markers (indicators of muscle mass, muscle strength, walk speed, and muscle quality, which is the true quantity of muscle that is able to generate optimal force) that would allow for better diagnosis and more effective evaluation of prospective treatments. The need to clarify the nature of the muscle–fat interaction and the relationship between sarcopenia and obesity was also emphasized, and the new phenomenon of sarcopenic obesity, which is a pathological condition of adipose mass (fat) gain with concomitant lean muscle mass/function loss, was presented.

Common Mechanisms Influencing Bone and Muscle Mass-'Pleiotropy'

There is a clear evidence for musculoskeletal pleiotropy (when a single gene influences more than one phenotypic trait), where bone and muscle would share genetic determinants during aging. Under this view, osteoporosis and sarcopenia would be different tissues' manifestation of the same process, dictated by common genes/protein modifications. Genome-wide associated studies have been used to study the genetic pleiotropy between bone and muscle,[6] and several genes,

including myostatin (*GDF-8*), *MEF-2C* and *PGC-1α*, have already been identified as promising candidates. Myostatin, a member of the TGF-β superfamily, is a negative regulator of muscle mass and performance. It has also been shown to be a fundamental factor in bone–muscle pleiotropy, as shown by studies linking muscle mass and bone structure (it is interesting to note that, although not discussed in this session, there is also an evidence of a role for myostatin in tendon development.[7] It was agreed that a better understanding of the cross talk between bones and muscles is essential to provide a basis for the study of these complex pleiotropic bone–muscle relationships. Furthermore, muscles and bones are endocrine organs that secrete factors that can influence distant organs. It would be unexpected for these tissues not to influence each other at the biochemical level. The question raised by the panel in this section was: should we study them together rather than in parallel? And what about tendons? They are certainly strategically positioned as loading and unloading is done through tendons, and they function as energy storage devices and even assist for skeletal muscles to generate force.[8,9]

Defective Mechanotransduction and Repair

Several key questions provided the framework for this session. Is the mechanosensitive intracellular signaling that is stimulated by exercise similar to all tissues of the musculoskeletal system? Which signals follow injury? How do the sources of stem cells change with aging?

Continued use and development of experimental models of musculoskeletal disuse and unloading can provide key new insights into how tissues respond to reduced mechanical loading. It is crucial to understand the dramatic musculoskeletal tissue loss of mass and function in spaceflight, despite regular exercise in-flight.[10] It is also critical for subjects in life-long non-weight-bearing situations, such as veterans in need of prostheses and patients who are immobilized. It is important to consider that bone and muscle are affected differently by altered load, and that, in both cases, changes in mass are not consistently related to changes in function. This suggests that bone–muscle interactions are much more complex in nature than previously considered.

Part of the discussion in this session focused on the importance of not only the intensity of the applied mechanical load but also its frequency for tissue response. For example, it has been shown that bone's sensitivity to mechanical signals increases with frequency, and extremely small accelerations can enhance bone regeneration.[11] Looking into the role of muscle cells in bone healing, we learned that there is a large gap that needs to be filled. For example, in non-union fractures very little is known about the stem cells involved in regeneration. Particularly, the difficulties in harvesting these stem cells limit our ability to study them. In addition to periosteal stem cells, it is believed that muscle-derived stem cells are important for bone regeneration based on multiple evidence including that fracture healing can be negatively affected by concomitant soft tissue injury. Why do fractured bones covered with skeletal muscles recover faster than those not surrounded by muscles? Similarly, it is equally important to have a better understanding of the complex process of heteroctopic ossification, particularly in injured skeletal muscles. Recent research has shown that after trauma, muscle may become responsive to the osteogenic effects of BMPs.[12,13] Certainly, the growth of bone in muscle is highly undesirable, but if we learn the aggressive mechanisms underlying this phenomenon, perhaps such knowledge could be used for bone repair or even prevention of osteoporosis.

Emerging Areas

Osteocalcin and the regulation of muscle mass. Does bone regulate any aspect of muscle biology? Bone is an endocrine tissue, and one candidate for a bone specific molecule is osteocalcin, an osteoblast-derived hormone.[14] Osteocalcin binds to the GPRC6A receptor and is known to affect adipocytes and β-cells in the pancreas. Osteoblasts also express the *Esp* (osteotesticular phosphatase) gene that inhibits osteocalcin function. What do knockout animal models tell us? Fascinating new data reveal that *Gprc6a*$^{-/-}$ mice have decreased muscle mass, whereas *Esp*$^{-/-}$ mice have increased muscle mass strongly, suggesting a role for osteocalcin in muscle mass regulation and its potential relationship to sarcopenia as further evidenced by its role in muscle regeneration. In addition, it has been recently reported that serum levels of osteocalcin increase with exercise.[15] Altogether, these results suggest that bone while affected by aging may also have a function of delaying the aging effects on muscles and other organs.

Muscle as an endocrine organ. Evidence that muscle is an endocrine organ comes from the regulation of glucose metabolism by interleukin-6 (IL-6) and a host of identified muscle-derived factors with systemic effects, making these myokines potential targets for the treatment of obesity-induced metabolic disease. One myokine that has been considered was the ciliary neurotrophic factor (CNTF), a member of the IL-6 superfamily; however, in a randomized multicenter clinical trial, participants developed antibodies to genetically engineered recombinant CNTF.[16] As a consequence, efforts to establish the viability of CNTF as a treatment of obese-related metabolic disease were discontinued. Despite this first frustrating result, genomic and proteomic screening of skeletal muscles are under way to identify new myokines that could be used in the treatment of those metabolic diseases.

The Wnts in bone–muscle cross talk. We were reminded that Wnts are essential for bone and muscle development, and that the role of Wnts in skeletal muscle after muscle development has been largely ignored. Intriguing new data on the effects of secreted factors from osteocytes on muscle cells and vice-versa was shared. Muscle factors stimulate the Akt-signaling pathway and protect osteocytes from dexamethasone induced apoptosis, while osteocyte secreted factors promote myogenic differentiation.[17,18]

An exciting future for bone–muscle cross talk is ahead of Us. The meeting ended with a panel formed by NIH Program Directors and all session chairs that discussed the future of bone–muscle research and the potential NIH grant mechanisms that will support muscle–bone interaction studies. This emerging and exciting new field is here to stay and promises to advance not only our knowledge of the BTM unit, but most importantly, it promises to identify new cures for chronic and devastating diseases.

Conflict of Interest

The authors declare no conflict of interest.

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