Citation: IBMS BoneKEy **11**, Article number: 515 (2014) | doi:10.1038/bonekey.2014.10

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MEETING REPORT

Cutting edge discoveries in muscle biology, disease and therapeutics (ASBMR 2013)

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IBMS BoneKEy **11,** Article number: 515 (2014) | doi:10.1038/bonekey.2014.10; published online 19 February 2014

Meeting Report from the 35th Annual Meeting of the American Society for Bone and Mineral Research, Baltimore, MD, USA, 4–7 October 2013

Introduction

Sarcopenia and osteoporosis are two major disorders of aging that are tightly associated in the frailty syndrome.[1] Their prevalence has increased during the past 3–4 decades in developed countries. It is estimated that up to 50% of the elderly population is osteoporotic and sarcopenic, with increased risk of falls and fragility fractures. This makes musculoskeletal diseases one of the most common causes of chronic disabilities. There is a growing interest in the research community to study the interaction between muscle and bone homeostasis, as attested by the number of publications during the past 5 years and the number of participants at this symposium '591'. Recent progress has been made in the cross-talk between muscle and bone, however, the precise mechanisms orchestrating the reciprocal adaptation in bone and skeletal muscle mass/function remain unclear. The aim of this symposium in the 35th ASBMR annual week was to review recent discoveries in muscle biology and pharmacology and to highlight the multiple potential interactions between these two tissues. The ultimate goal of the meeting was to generate a better understanding of the tight communication between muscle and bone throughout development, growth, aging and disease in order to identify new therapeutic targets.

The workshop had been designed by an organizing committee constituted of Pr Lynda F. Bonewald, Pr Kevin Conley and Pr Karyn Esser. The learning objectives from the meeting were to (1) identify the cells of muscle and understand how they function under normal and pathological conditions; (2) identify the functions of muscle beyond contraction, such as calcium regulation, metabolic cross-talk with glucose metabolism, thermogenesis and myokine; (3) understand what happens to human muscle with age; (4) understand the cross-talk between the muscle and the kidney; and (5) understand the relationship of exercise to sarcopenia.

Morning Session 1: 'The Cells of Muscle'

Kardon G, University of Utah, presented studies in mice genetically ablated for satellite cells, by using $Pax7^{Cre}$ mice, or for fibroblasts, by using $Tcf4^{Cre}$ mice crossed with $R26R^{DTA}$. Their work supports the evidence that satellite cells are required for muscle regeneration and also identify fibroblasts as novel and vital components of the niche regulating satellite cell expansion during muscle repair. They particularly show that ablation of fibroblasts specifically alters the dynamics of satellite cells leading to premature satellite cell differentiation, and therefore smaller myofiber regeneration. This interaction suggests that therapeutic treatments to reduce fibrosis in the context of muscle diseases and/or aging need to be carefully administered in order to avoid interfering with early pro-regenerative interaction between fibroblasts and satellite cells. Brack A, Massachusetts General Hospital, illustrated the potential role of satellite cells and their association with tissue fibrosis in the decline of skeletal regeneration with age. He showed that muscle stem cells from aged mice tend to convert from a myogenic to a fibrogenic lineage and that this conversion is mediated by different factors such as Notch, FGF-2 and canonical Wnt signaling. Surprisingly, during aging the activation of Wnt signaling inhibits myogenesis, contrasting with the classical knowledge that Wnt signaling promotes myogenic lineage progression as observed during development. With the development of sclerostin-neutralizing antibodies for the treatment of metabolic bone disorders, these observations on Wnt signaling in muscle raise questions concerning its potential effects on muscle function.

Goldhamer D, University of Connecticut, examined whether muscle satellite cells represent a source of osteogenic cells during heterotopic ossification. The most severe form of heterotopic ossification is manifested as a rare autosomal dominant genetic disorder, fibrodysplasia ossificans progressiva (FOP), resulting from mutations in glycine–serine regulatory domain of the BMP type 1 receptor. They first demonstrate that contrary to what we think, endothelium does not detectably contribute to BMP2-induced skeletogenesis in the mouse. And second, those multipotent mesenchymal cells resident in the skeletal muscle interstitium are the predominant source of progenitors that drive heterotopic ossification.

These presentations provide fertile thinking for future studies to improve tissue repair, particularly under conditions in which regeneration is impaired and fibrosis is favored, such as in aging

muscle and bone. Moreover, they emphasized that satellite cells possess mesenchymal plasticity, being able to commit either to the myogenesis, skeletogenesis or adipogenesis program depending on the environment.

Morning Session 2: 'Function Beyond Contraction'

Esser K, University of Kentucky, reported results in *Bmal-1*$^{-/-}$, *Clock*Δ*19* and *MyoD*$^{-/-}$ mice suggesting that MyoD, that is, a master regulator of myogenesis, may act as a molecular link between the circadian clock and skeletal muscle maintenance. They particularly show that *Bmal-1*$^{-/-}$ mice are good models of accelerated aging with profound mitochondrial pathologies associated with myofilament size, structure and contraction properties. These results show that MyoD is a clock-controlled gene, and define the circadian factors CLOCK and BMAL1 as critical modulators of molecular, cellular and functional parameters of skeletal muscle. The molecular clock is therefore a potential important factor in the interaction between muscle and bone tissue occurring throughout life. Neufer D, University of East Carolina, focuses on linking mitochondrial bioenergetics to insulin resistance via redox biology. Decreased insulin sensitivity in skeletal muscle is a primary factor in the etiology of type 2 diabetes. To explain insulin resistance, mitochondria function/dysfunction has been placed at the center of a theory. The speaker illustrates this theory by showing that fuel excess, more specifically excessive fat oxidation, increases mitochondrial production (acylcarnitine) and emission (H_2O_2), leading to the development of insulin resistance. This presentation is of importance in view of the increasing incidence of obesity and diabetes in all western countries and the disability associated with the metabolic syndrome. It suggests that efforts must be directed at prevention in children and young adults against nutritional overloads rather than waiting for a magic pill.[2]

Cornelison D, University of Missouri, showed the important role of muscle satellite cell motility during development and muscle repair, and their ability to respond to multiple guidance cues. Through strip assay and very impressive real-time microscopy imaging *in vitro*, they demonstrate the ability of these cells to sample their environment and the other cells presented in the damage regions. They specifically illustrate that multiple ephrins elicit a repulsive migratory response in satellite cells, and that these ephrins are differentially present on the surface of healthy and regenerating myofibers. This suggests a potential not only for ephrin signaling but also for other juxtacrin signaling such as semaphorins to mediate guidance of satellite cells, which would secondarily impact multiple steps of muscle regeneration.

These presentations reinforce the close analogy between muscle and bone function with—first, the involvement of clock genes as common muscle and bone promoter;[3] second, the importance of redox system in the etiology of insulin resistance, sarcopenia and osteoporosis;[4] and finally, the importance of cell mobility and role of factors involved in cell interaction such as Ephrins.[5]

Afternoon Session 1: 'Clinical Application of Muscle Wasting and Disease'

Conley K, University of Washington, underlined that with age, mitochondrial alteration of electron assembly transport chain results in damage in the pumping of protons. Hence, proton-motive force assessment may underlie some age-associated metabolic abnormalities and can be considered as a new biomarker. He shows that delta-pH of mitochondrial activity levels was negatively associated with muscle size and function, and was therefore a good indicator of healthy mitochondria. Himmelfarb J, University of Washington, investigated the relationship between muscle wasting and chronic kidney disease (CKD). Similar to sarcopenia of aging, the muscle wasting of CKD may be associated with mitochondrial dysfunction that raises questions about the role of mitochondria in the development of uremic complications. Interestingly, myopathy changes in CKD can be reversed with resistance exercises that enhance mitochondrial function, improve muscle fibers and muscle mass, and contractile function. Contributions of signaling pathways activated or inhibited during exercise (IGF-1/PI3K/Akt/mTOR/Myostatin/Smad2/Smad3…) have not been challenged in the discussion, raising the question whether they bear some similarity to those involved in the bone response?[6]

Damon B, University of Vanderbilt, summarized all the possible evaluations of muscle structure and function through imaging techniques. He particularly underscored the advantage of MRI to evaluate mass, structure, strains, vascular system and its ability to discriminate different metabolic diseases.

Afternoon Session 2: 'Therapeutics'

Various muscle therapeutic strategies have been started to direct anabolic effects (androgen), anti-catabolic (anti-myostatin, anti-inflammatory) and functional improvements (phosphodiesterase inhibitors). Guttridge D, University of Ohio, focused on the role of NF-kB inhibitors (NBD = Nemo inhibitor of NF-kB) on skeletal myogenesis in muscular dystrophy. Historically, in 2003, NF-kB was identified in skeletal muscles of Duchenne muscular dystrophy (DMD) patients and in MDX mice. In 2005, inhibition of the NF-kB pathway reduced skeletal muscle damage and enhanced muscle function in the MDX mice and more recently in a dog model of DMD. NBD peptide is currently poised to move forward into clinical trials. Roubenoff R, University of Tufts, presented a review of the current knowledge on the regulation of myostatin, that is, the molecular rheostat for muscle mass, and discussed its implications in the development of therapeutic agents to combat muscle loss. Myostatin is a member of the transforming growth factor-beta (TGF-β) family and it binds to two activin type II receptors, ACVR2 and ACVR2B, which then leads to binding and activating of type I receptors, ALK4/5. The myostatin pathway activates Smad 2/3/4 that results in the inhibition of muscle growth. Myostatin inhibitors have been found to be rapidly promising in the MDX mouse model by increasing fiber numbers and sizes and therefore muscle mass and contractile force. Interestingly, few investigations show that myostatin inhibitors have a proper role on bone.[7] However, trials revealed that myostatin inhibitors present some adverse effects such as gum and nose bleeds. Extensive efforts are also being made to develop new effective strategies by targeting myostatin signaling modulators such as follistatin, activin receptor inhibition, GASP-1 and -2, and LTBP-3.[8]

The symposium also highlighted the prominent support from the National Institutes of Health to this field with the presentation

of the FNIH biomarkers consortium sarcopenia project. Its mission is to create an overview of sarcopenia developments and thereby improve sarcopenia definition, analysis, diagnosis and clinical therapeutics. Compared with the bone field, which already benefits from several drugs against osteoporosis, the muscle field suffers from a non-precise definition of sarcopenia that has delayed the therapeutic progress. Roubenoff R, University of Tufts, estimates that muscle is the last drug-able system that as yet does not have a specific drug.

Conclusions and Remaining Questions

During this journey, more than 109 posters from basic research to clinical trial have also been presented, allowing an exchange of ideas and discussion for initiation of new collaborations. The presenters developed strong arguments to demonstrate that basic and clinical research on muscle biology and disease presented high homology with bone tissue. Interestingly, the topics of this symposium emphasized the reciprocal influence of muscle on bone, similar to what was reported a few years ago between fat and bone. The integration of muscle, bone and fat metabolism in the understanding of aging and metabolic diseases is a requisite for efficient and safe drug development. This symposium identified high-priority areas for future studies by asking new questions:

- How can we control satellite cell proliferation, differentiation and mobility?
- How can we impact mitochondria of a specific tissue without affecting the others?
- What is the contribution of fat in the muscle–bone homeostasis?
- Are imaging techniques or biomarkers precise, specific and reproducible enough for the diagnosis of sarcopenia?
- Considering the close association of bone and muscle during development and aging, could we speculate for the existence of a coupling factor or pleiotropic genes in both tissues? Can it open therapeutic options for the common treatment of osteoporosis and sarcopenia?
- Can fat and muscle factors be a target for treating osteoporosis?

Conflict of Interest

The author declares no conflict of interest.

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