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Editorial overview: Muscle and bone are highly effective communicators

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Joan M. Taylor, PhD, is Professor and Vice Chair for Research in the Dept. of Pathology and Associate Director of the McAllister Heart Institute at the University of North Carolina at Chapel Hill. The overall goal of Dr. Taylor's research is to characterize the intracellular signaling pathways that govern normal and aberrant growth responses in the cardiovascular and musculoskeletal systems.

Cell types comprising skeletal muscle and bone have long been known for their remarkable communication skills. Indeed, cellular communication in the musculoskeletal system is essential for appropriate growth and remodeling necessary to both generate and transmit force and to appropriately respond to the tremendous repetitive load-induced pressures imparted on these tissues. However, more recent studies indicate that self-control is only part of the equation. For example, it is now clear that skeletal muscle and bone play important roles in both short (autocrine, paracrine) and long range (endocrine) communication processes that control myriad events including, but not limited to, regulation of angiogenesis, local and systemic inflammation, organismal metabolism, brain function, cardiovascular health, and aging. The review articles in this issue discuss the numerous factors (cytokines, peptides, miRNAs and metabolites) known to be released from skeletal muscle and bone, their local and systemic effects and how the release of these factors is regulated at the tissue, cellular, and sub-cellular level.

Skeletal muscle development and homeostasis involves complex communicative interactions between satellite cells, myoblasts and myotubes. As emphasized by Demonbreun and McNally in this issue, both myoblast fusion to form multinucleated myotubes and myotube repair is governed by localized deposition of fusogenic membrane lipids (i.e. PIP2) and fusogenic proteins [1]. Critical fusogenic proteins include the transmembrane protein myomaker and membrane anchored ferlin family members myoferlin, Fer1L5, and dysferlin. Ferlins are only transiently expressed on muscle plasma membranes and their active recruitment to the sarcolemma is tightly regulated by endocytic recycling [2,3]. While a complete understanding of how such proteins are deposited to future sites of cell to cell fusion or membrane repair is lacking, it is clear that both cytoskeletal remodeling and vesicle trafficking by the BAR/PH-domain containing GRAF family of RhoGAPs is involved. Indeed, our groups have shown that GRAF1 is necessary and sufficient to drive robust myoblast fusion and/or membrane repair by facilitating the 'capture' of ferlin-containing endocytic vesicles at the plasma membrane [4–6]. Our studies support a model in which the GRAF1 is recruited to phosphatidyl serine enriched pre-fusion complexes on the plasma membrane through its PH domain wherein its RhoGAP domain facilitates clearing of sub-plasmalemmal actin and its membrane curvature sensing BAR domain binds to and facilitates the capturing ferlin-containing endocytic vesicles. As several muscular dystrophies are associated with abnormal plasma membrane localization of ferlins [7,8] a more detailed understanding of these trafficking events could lead to new therapeutic avenues to mitigate the pathological progression of these morbid diseases.

Secretion of soluble autocrine factors and exosomal proteins/miRNAs are additional modes of communication utilized by muscle cells to regulate skeletal muscle growth, regeneration, and repair. Likewise, as reviewed by Park et al in this issue, bone formation and remodeling is dynamically controlled by bi-directional autocrine communication between bone forming osteoblasts and osteocytes and bone remodeling osteoclasts [9]. Moreover, as highlighted by both this group and Giudice and Taylor in this issue, the peptides and cytokines released from muscle and bone can influence whole body homeostasis and the pathological progression of numerous diseases [9,10]. Once again, at the cellular level such para- and endocrine communication is largely achieved by vesicle trafficking events and these reviews delve into the diverse stimuli that govern these processes. Notably, recent advances in proteomics have led to the identification of over 300 bone fide 'myokines' or peptide-based factors released from muscle cells. Approximately 80% of these factors are predicted to be secreted via conventional Golgi-PM trafficking of secretory vesicles, while others (that lack N-terminal signal sequences) are released in micro-vesicles or exosomes. As discussed by Giudice and Taylor, surprisingly few of the peptides and cytokines identified to date in the myo- or osteo-secretome are tissue selective [10]. This small list includes the myokine irisin that is released by skeletal muscle in response to exercise and has profound beneficial effects on bone growth and osteocalcin, a bone-specific hormone, which promotes metabolic health by stimulating insulin secretion from islet cells and adiponectin secretion from adipose tissue. Other beneficial myokines including the cytokines IL-6 and IL-15 are secreted by various cell types, but given that skeletal muscle is the largest organ in the human body, coupled with the finding that plasma levels of these factors dramatically increases (up to 100 fold) after exercise indicates the likelihood that muscle is a major contributor to circulating levels of these factors [11–13]. Additional myokines discussed in this issue that have long ranging actions on myriad target tissues include, but are not limited to broadly expressed growth factors such as fibroblast growth factors 2 and 21, Insulin like growth factor-1 (IGF1), folliostatin like 1 (FSTL-1), musclin, and apelin. These factors act on a remarkable number of target tissues and have been reported to restrict obesity, insulin resistance, type 2 diabetes, and have broad salutary effects on the cardiovascular system, brain, and skin. Ultimately, the endocrine functions of skeletal muscles are thought to be largely causal for the beneficial effects of physical activity. Nonetheless, the future skeletal muscle selective depletion of such myokines in genetically engineered animal models is needed to confirm this contention.

While the clinical benefits ascribed to the paracrine/endocrine factors released by muscle and bone are far reaching, many questions remain with respect to the physiological and/or pathological responses that control their release. Cytokines and peptides synthesized in the ER that contain a signal peptide are released through the classical secretory pathway that involves centrifugal trafficking followed by the docking and fusion of intracellular vesicles with the PM [14]. Secretory vesicles are initially formed in the peri-nuclear trans-Golgi network and are transported towards specific regions of the PM along cytoskeletal elements that include actin/myosin myofilaments, microtubules (MTs), or intermediate filaments (IFs). Recent studies indicate that the specific "highway" used differs between cells [15] and since differentiated muscle and bone cells have distinctive cytoskeletal structures, vesicle transport, docking, and release are likely coordinated in a unique fashion in these cells, yet this is an understudied area in the field.

As described in the review by Jiao and Demontis in this issue, the mechanisms that govern exosome release from bone and muscle are even less clear although recent data indicates that autophagy related pathways are involved [16]. Skeletal muscle cells are highly metabolically active and as such are particularly dependent on macroautophagy (hereafter referred to as autophagy) for energy production and removal of damaged organelles or misfolded proteins. While too much or too little autophagy can be detrimental, Demontis et al showed that a modest increase in basal autophagy in fruit fly skeletal muscle prevented age-related muscle dysfunction and extended lifespan [17]. Interestingly, recent studies indicate that degradative autophagy also impacts the muscle secretome. The term "secretory autophagy" has been used to describe a direct role for autophagy in mediating the extracellular delivery of leaderless proteins, microbes, aggregation prone proteins, and damaged organelles through autophagy intermediates. While extrusion of such components is intrinsically beneficial to the cell, secretory autophagy may have a net negative effect on tissues, as many of the cargo (mitochondria, ATP, α-synuclein, HSP60, etc.) would be expected to trigger the innate immune response [18]. As well, many of the non-leaderless proteins released via secretory autophagy -as defined by the dependence of their secretion on a subset of autophagy-related genes (Atg)- are pro-fibrotic. To date, this list includes IL-1b, IL-18, HMGBI, and Galectin-3. [19]. That said, both bone-derived and muscle-derived exosomes also carry numerous microRNAs which have been shown to have a positive impact on bone and muscle development and remodeling [1,9]. Many mechanistic questions remain including: what are the precise vesicle carriers for these distinct cargo? How are such carriers are transported/docked at the PM, and at what level do these pathways diverge from the degradative autophagy and/or converge with conventional secretory vesicle trafficking? The finding that at least some cargo including IL-1β and α-synuclein can either be substrates for autophagic degradation or secretion and