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Bone and Skeletal Muscle: Neighbors With Close Ties

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Abstract

The musculoskeletal system evolved in mammals to perform diverse functions that include locomotion, facilitating breathing, protecting internal organs, and coordinating global energy expenditure. Bone and skeletal muscles involved with locomotion are both derived from somitic mesoderm and accumulate peak tissue mass synchronously, according to genetic information and environmental stimuli. Aging results in the progressive and parallel loss of bone (osteopenia) and skeletal muscle (sarcopenia) with profound consequences for quality of life. Age-associated sarcopenia results in reduced endurance, poor balance, and reduced mobility that predispose elderly individuals to falls, which more frequently result in fracture because of concomitant osteoporosis. Thus, a better understanding of the mechanisms underlying the parallel development and involution of these tissues is critical to developing new and more effective means to combat osteoporosis and sarcopenia in our increasingly aged population. This perspective highlights recent advances in our understanding of mechanisms coupling bone and skeletal muscle mass, and identify critical areas where further work is needed.

Keywords

MUSCLE; BONE; INTERACTION; OSTEOPOROSIS; SARCOPENIA

Introduction

The musculoskeletal system is of paramount importance in our daily lives. In addition to the commonly identified actions of bone and muscle to support upright stance, facilitate movement and breathing, and serve as a protector of our internal organs, these tissues also serve critical metabolic roles. Bone serves as an internal reservoir for calcium to ensure the proper function of nerves and muscle,[(1)] and skeletal muscle is responsible for over 80% of carbohydrate storage.[(2)] Recent studies suggest that the skeleton also contributes to glucose homeostasis, further intertwining the actions of bone and muscle beyond locomotion.[(3)]

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Mammalian bone and skeletal muscle involved with locomotion develop in close association from the somitic mesoderm, and accumulate their final adult mass according to specific genetic instructions and environmental cues. Changes in muscle and bone mass brought about by exercise, disuse, or aging are also tightly correlated in both humans and experimental animal models. However, the precise mechanisms responsible for this synchronization remain unclear. It has been widely assumed that coordination of muscle and bone mass occurs through muscle force-generated mechanical signals, which transduce anabolic activity in the adjacent bone.[4] Indeed, evidence from human and animal studies supports the role of mechanical signals as a factor coordinating muscle and bone volume, as is discussed in detail here. The shared mesodermal origin of muscle and bone[5] presents an additional possibility; that common molecular networks serve to coordinate their mass.[6–11]

Clearly, a better understanding of how muscle and bone synchronize their mass throughout life is critical to the development of more effective strategies to improve musculo-skeletal health and function. In this regard, many of the studies we review herein suggest a dominant role of muscle over bone in synchronizing the mass of these two tissues (at least in postnatal life). Such a hierarchy of control in synchronizing the musculo-skeletal system, if brought to bear through additional study, could completely shift our paradigm for treating osteoporosis and frailty. In this perspective, we review recent findings regarding the mechanisms that coordinate the mass of muscle and bone—from early development through aging and involution—and discuss how these data might help guide our approaches to treating disorders in both tissues.

Developmental Biology of the Musculoskeletal System

Locomotion in vertebrates requires muscles to contract and work against the levers of an internal skeleton, enabling the movement of body parts. The vertebrate skeleton is composed of bone and cartilage linked to skeletal muscle through tendons (for an excellent review of tendons in musculoskeletal development see Schweitzer and colleagues[12]). The skeleton forms in a discrete stepwise process initiated by condensation of mesodermal mesenchymal precursors at the future sites of bone. Following condensation, these precursors differentiate into chondrocytes to form a cartilage anlage (endochondral bone formation) or directly into osteoblasts to form bone (intramembranous bone formation), depending upon positional cues.[13] Once formed, the skeleton is continually remodeled throughout life, which allows for repair of microdamage and adaptive response to increased or decreased mechanical loads. The process of bone remodeling is achieved by the coordinated actions of the bone-forming osteoblasts, bone-resorbing osteoclasts, and osteocytes—terminally differentiated cells of the osteoblast lineage that are embedded in mineralized bone and appear to serve a multitude of functions including mechano-sensation, regulating bone remodeling (via receptor activator of NF-kB ligand [RANKL] and Sclerostin), and participating in phosphate homeostasis (via fibroblast growth factor 23 [FGF23]).[14] The rate and degree of coupling of bone formation to resorption during remodeling is regulated by autocrine, paracrine, and endocrine factors including, but not limited to, Wnts, Hedgehog, and Notch, bone morphogenetic protein (BMP) families, transforming growth factor-β (TGF-β), growth hormone (GH), and insulin-like growth factor-1 (IGF-1), FGF-2, interleukin-6 (IL-6) type cytokines, and ephrinB2 and B4.[15]

Myogenesis occurs immediately adjacent to, and concurrent with, the development of the skeleton during embryogenesis. In the case of skeletal muscle in the trunk and limbs, precursors from the paraxial mesoderm differentiate and fuse to form multinucleated syncytia, or myofibers, that comprise skeletal muscle.[16] Specification of mesodermal precursor cells into the myogenic lineage occurs in the somite for limb muscles, under the control of Pax3/7.[17] Signals from surrounding tissues then increase myoblast expression of myogenic factors (*Myf5/MyoD*) and drive further differentiation and myogenesis.[17,18] During primary myogenesis, myoblasts fuse to form nascent myotubes, with relatively few nuclei. Secondary myogenesis is characterized by subsequent recruitment and fusion of additional myoblasts and ultimately gives rise to the multinucleated, mature myofibers. However, it would appear that not all *Myf5/MyoD* expressing myoblasts fuse. Muscle satellite cells (which are Pax7-positive and recently demonstrated to have previously expressed *Myf5* and *MyoD*) can first be observed under the basal lamina of muscle fibers in late fetal stages. These satellite cells do not divide and remain on the periphery of the myofibers to serve as the source of new myonuclei during postnatal growth and injury repair.[17,18] Similar to the regulation of bone development and mass, skeletal muscle development and maintenance is regulated by morphogens and growth factors, many of which overlap with those involved in skeletogenesis, such as Wnts, Hedgehog, Notch, FGFs, IGF-1, and TGF-β.[16] Among the most dominant factors controlling muscle size is myostatin, a member of the TGF-b superfamily. Myostatin negatively regulates skeletal muscle size by activating ACVR2B and initiating Smad2/3 signaling.[19,20]

Many of the overlapping signaling pathways present in muscle and bone development exert similar functions in both tissues. For example, GH and IGF-1 increase proliferation and differentiation of both osteoblasts[21] and myoblasts[22] during development in mice. Some differences are apparent, however, in the activity of these growth factors between muscle and bone. GH appears to uniquely interact with sex steroids in determining the sexually dimorphic patterns of the skeleton.[23]

Wnt signaling is also critical for the development of both muscle and bone and exhibits significant overlap in function between the two tissues. In muscle, Wnts control myogenic regulatory factor (MRF) expression during early embryogenesis to initiate the myogenic program, as well as regulating satellite cell differentiation, self renewal, and muscle fiber growth in response to loading (the latter two through noncanonical signaling) in adult life.[24] Similarly in bone, Wnt signaling is critical for the specification of mesenchymal progenitors toward the osteoblast lineage and responding to mechanical loading.[25] Interestingly, the precise control of Wnts in regulating development seems to be dependent upon timing of exposure in bone,[25] whereas in muscle, the level of Wnt signaling seems to be the primary modulator.[24] A better understanding of the molecular bases underlying the divergent roles in these common signaling pathways of muscle and bone might reveal novel therapeutic targets.

The close physical linkage of bone and muscle development is evident even before birth. For example, the varying circumferential shape of different long bones occurs through asymmetric mineral deposition, apparently in response to site-specific mechanical strains applied to the newly forming bones by their associated muscle groups in utero.[26] In

agreement with this notion, the shapes of long bones from muscular dysgenesis (mdg) mice, which lack muscular contraction due to an excitation-contraction coupling defect, are nearly uniformly circular and mechanically inferior to those of normal mice. Muscular contraction during embryogenesis has also been demonstrated to be critical for maintaining specification of joint progenitors to ensure proper joint morphogenesis. A study from Kahn and colleagues[27] noted the loss of elbow, midcarpal, and hip joints in three different mutant mice that lacked muscle, as well as the mdg mice described in the study by Sharir et al.[26] Evidence supporting the importance of muscular contraction for proper skeletal development can also be observed in rare neuromuscular disorders that reduce human fetal muscle contraction. Fetal immobilization secondary to congenital myotonic dystrophy or spinal muscular atrophy resulted in thin, hypomineralized, and elongated long bones with multiple fractures.[28,29] In addition to mechanical crosstalk during embryogenesis and fetal development, recent evidence suggests bone and muscle development are intimately linked through morphogen signaling. In both mouse and chick embryos, bone-derived Indian hedgehog (Ihh) promotes fetal myoblast survival and secondary myogenesis.[30] Importantly, the ability of bone-derived Ihh to support myogenesis indicates that muscle-bone crosstalk is bidirectional.

Postnatal Coordination of Bone and Muscle Mass

During postnatal growth in mammals, bone and muscle mass increase dramatically and proportionally, achieving peak mass at around the same time (25–35 years old in humans).[31] Longitudinal growth of long bones occurs through endochondral ossification.[32] The growth plate generates a cartilaginous template that becomes new trabecular bone, elongating the metaphysis. Trabeculae near the outer edges of the bone eventually coalesce to form the metaphyseal cortex. As the bone elongates, those trabeculae near the center of long bones are resorbed to form the marrow cavity. In the diaphysis, cross-sectional growth is mediated by the combination of periosteal cortical apposition and endosteal resorption. The postnatal growth of muscle results entirely from an increase in muscle fiber size (hypertrophy), although the mechanism(s) driving this process has been widely disputed. Muscle hypertrophy had long been thought to require the proliferative activity of satellite cells and their fusion with existing muscle fibers,[33–35] but recent evidence has demonstrated hypertrophy of muscle fibers in the absence of satellite cells.[36]

Genetic background

A fundamental determinant of peak bone and muscle mass is genetic background. Bivariate linkage analysis in large human populations has identified significant quantitative trait loci (QTLs) shared by leg lean mass with shaft cross-sectional area on chromosome 12p12–12p13 and with neck shaft angle on 14q21–22.[37] Another study of 102 monozygotic and 113 dizygotic older female twin pairs demonstrated shared genetic components in muscle cross-sectional area of the lower leg, bending strength of the tibial shaft, and compressive strength of the distal tibia from pQCT scans.[38] Analogous studies in animal models also indicate that common gene subsets control bone and muscle mass. For example, inactivating mutations of myostatin cause hypermuscularity in mice, with increased cortical bone mineral content (BMC) at the L_5 vertebra, larger spinous processes, and larger entheses on

the femur and humerus.[39,40] It has also been proposed that genetic background might determine responsivity of the muscle-bone unit to mechanical stimuli. In support of this idea, Lang and colleagues[41] used structural equation modeling to examine the extent to which select genetic loci manifest their pleiotropic effects in the musculoskeletal system through adaptation to mechanical stimuli. Genetic analysis in male and female F2 offspring from a B6XD2 intercross demonstrated correlations among bone strength, muscle mass, and physical activity, and identified several QTLs associated with mechanosensitivity.

Sex steroids

Superimposed on these genetic determinants of bone and muscle mass are anabolic stimuli that occur postnatally, the most dominant of which is puberty. During the pubertal growth spurt, bone and muscle mass accumulate rapidly under the influence GH, IGF-1, and sex hormones.[42] Pubertal increases in lean body mass are detected prior to increased BMC, suggesting that skeletal mass increases to accommodate stresses incurred from increased muscle force.[43] In agreement with this concept, tibial cross-sectional moment of inertia is tightly correlated with the cross-sectional area of the calf muscles.[44] Although females enter puberty first, males have a longer pubertal growth spurt and greater peak longitudinal growth velocity than females, which ultimately results in 10% greater height and 25% greater peak bone mass in males.[45] In addition, male bones attain a larger diameter due to greater periosteal expansion and less endocortical apposition than females.[46,47] These sex-specific differences in skeletal acquisition are mediated by the differential effects of androgens and estrogen.[48] Peak muscle mass is also higher in males[49,50] as a result of the well documented anabolic effects of androgens in muscle hypertrophy (in both sexes) commonly observed in professional bodybuilding. Additionally, testosterone increases muscle mass and strength in hypogonadal men[51] and normalizes the reduced muscle mass in orchidectomized rodents.[52] By contrast, estrogen appears to have little direct effect on muscle hypertrophy, and replacement therapy fails to prevent loss of muscle mass and strength in aging females.[53,54]

Mechanical forces

In addition to the genetic determinants and humoral factors affecting musculoskeletal mass, and likely in direct interplay with them, the level of physical activity in which a human or animal engages plays a tremendous role in determining postnatal muscle and bone mass. Physical activity exerts anabolic effects on the skeleton either directly, indirectly through mechanical forces generated by muscle action, or indirectly through endocrine regulation (ie, elevation of GH and IGF-1), and understanding the precise mechanisms underlying this anabolic response is an area of very active research. Exaggerated examples of mechanical effects achieved though vigorous exercise are seen in the increased bone density of the dominant arm (which also has increased muscle mass) of premier racquet sport participants.[55–57] Thankfully for the majority, it appears that such benefits are not restricted to elite athletes. Both muscle and bone have recently been demonstrated to be responsive to low-magnitude mechanical signals.[58] Genetic linkage studies in mice have been performed to tease out genes that may be responsible for the anabolic response of bone to mechanical stimulation. For example, Kesavan and colleagues[59] performed QTL analysis after applying bending loads to the tibias of 10 week-old female F2 mice from a B6XC3H

intercross and identified several loci that appeared responsible for mechano-sensitivity. Whether these same genes exert such effects in muscle is a question that clearly warrants further investigation.

Conversely, disuse or unweighting of the muscle-bone unit in immobilized individuals (bed rest) or after space flight, respectively, results in a dramatic loss of bone and muscle mass.[60] In many cases, the loss of muscle appears to drive the loss of bone. For example, individuals with Duchenne muscular dystrophy and cerebral palsy—primary defects in muscle function—also have reduced bone mass and increased fracture risk.[61–64] Furthermore, significant bone loss occurs in patients with spinal cord injury (SCI)[65]; where rapid and profound muscle loss of muscle mass secondary to motor neuron loss is presumably the precipitating factor.[66] Additional evidence supporting a primary role for muscle as a determinant of bone mass comes from studies in subjects exposed to chronic unloading during space flight. Individuals exposed to zero gravity experience minimal neuromuscular mechanical stimulation (bodies in space have mass but not weight), with significant muscular atrophy and bone loss (1% of total muscle and 1.8% to 2% of total bone lost per month[60]). Interestingly, the losses of muscle and bone during space flight are far less pronounced in the upper extremities that do not typically bear weight, but myriad physiologic changes in space (cardiovascular, etc.) make interpretation of such findings difficult.

Other studies in microgravity, or in settings designed to minimize the effects of gravity, suggest that the variable effects of loading and unloading on different regions of the musculo-skeletal system may actually stem from its biomechanical evolution to protect joints against the force of gravity.[67] In this regard, the musculature of the human body can be largely anatomically divided into monoarticulate (muscles that cross a single joint) or biarticulate (muscles that cross two joints). In a complex movement, such as pedaling a bicycle, monoarticulate muscles generally maintain joint position while biarticulate muscles orchestrate the direction and force of leg movement.[68] Using a ballistic knee movement model, Richardson and Bullock[69] experimentally eliminated gravitational load cues from subjects' knee movements and demonstrated that biarticulate muscle recruitment increased with increasing speed, while monoarticulate muscles were unaffected. Conversely, activation of monoarticulate muscles in the knee and hip was significantly higher under weight bearing versus non–weight bearing conditions, with normal gravitational load.[70] This suggested the presence of an "antigravity" system within the musculature, particularly monoarticulate, to support and protect joints and maintain posture under gravitational load. Indeed, in conditions of microgravity, such postural muscles demonstrate the greatest losses of mass.[71,72] The loss of muscle mass from these postural muscles in unloaded conditions is also associated with fiber-type switching—from slow (endurance) to fast (easily fatigued) fibers.[73] Similar changes are also observed in cases of immobility and bed rest.[74] It should be noted that age-related fiber-type switching differs from that seen in microgravity or during bed rest; ie, the muscles that atrophy tend to be type IIX (fast) fibers with increasing dependence on type IIA (intermediate) and type I (slow) fibers.[75] Thus, it is reasonable to suggest that aging and bed rest simultaneously impinge upon two different fiber types, compounding the impairment of muscle function. The atrophy of postural and stabilizing muscles during a hospitalization (and switch to easily fatigued fast fibers) might

predispose an elderly individual to poor(er) posture and biomechanics, which could lead to joint damage or even falls (because the age-related switch from fast fibers would make it more difficult to compensate for a loss of balance), creating a vicious cycle of muscle and bone loss from further inactivity.

Experimental maneuvers to mimic unloading in rodents, such as tail suspension, can reproduce some of the effects of microgravity, including rapid loss of muscle and bone.[76] Interestingly, certain genetic strains of mice (C3H/HeJ) are resistant to unloading-induced bone loss.[77] These models are beginning to be used to examine the underlying genetic determinants of responsiveness of muscle and bone to unweighting, with obvious implications for identifying potential therapeutic targets to prevent muscle and bone loss associated with more “down to earth” problems like injury and immobility.

Aging and Musculoskeletal Involution

The mass of both skeletal muscle and bone are profoundly affected by age. Age-related muscle atrophy, referred to as “sarcopenia,” is characterized by the loss of both strength and skeletal muscle mass.[78] Muscle mass decreases by 3% to 8% per decade after age 30 years, and the pace of muscle loss only quickens after age 60 years.[79] This loss of muscle mass and strength is due to progressive atrophy, loss of muscle fibers, reduced motor neuron input, and impaired function of the contractile apparatus within each fiber.[80] Aging is further complicated by periods of bed rest or inactivity, due to an injury such as a hip fracture, which can result in profound losses of both bone and muscle in parallel.[81] In a sample of community-dwelling seniors, hospitalizations were associated with a loss of lean mass and fat mass, as well as a loss of strength in men.[82] Even in healthy older persons, 10 days of bed rest can produce losses of strength of over 13% along with losses of aerobic capacity.[83] Bed rest might also have deleterious effects on postural support that could predispose to joint damage and/or falls.[67] Although the declines in muscle can be partially explained by reduced physical activity with age, sarcopenia also involves metabolic abnormalities, including reduced insulin sensitivity, fat and connective tissue infiltration, impaired oxidative defense, reduced hormone levels, and decreased mitochondrial activity[84–86] that further confound muscle function.

At the cellular level, these sequelae of sarcopenia can disturb the already faltering balance of protein synthesis and degradation present in aging muscle. Muscle atrophy occurs through the concerted actions of numerous signaling pathways and molecular mechanisms (recently reviewed by Bonaldo and Sandri[87]) including insulin-like growth factor 1 (IGF-1)-Akt-mammalian target of rapamycin (mTOR)/Forkhead box O (FoxO), inflammatory cytokines and NF-kB signaling, myostatin/activin signaling, the ubiquitin-proteasome system, and the autophagy- lysosome system. Indeed, recent studies suggest that autophagy may play a significant role in sarcopenic muscle atrophy. Autophagy is critical in many cell types for the turnover of cellular components, both on a continual basis and in response to stress, nutrient deprivation, or cytokines.[88] Evidence of muscle diseases in states of both excess[89] and defective autophagy[90] suggest that there may be an optimum autophagy flux in muscle to maintain contractile function, and disruption of normal autophagy with age might predispose muscle fibers to chronic contractile damage and, eventually, atrophy.[91] As noted above,

mitochondrial function declines with age and results in progressive activation of autophagy to recycle these dysfunctional mitochondria, possibly causing just such a disruption in autophagy flux. In support of this notion, transgenic expression of peroxisome proliferator-activated receptor gamma coactivator-1a (PGC1a) in skeletal muscle (a master regulator of mitochondrial biogenesis) prevented the age-related increase in autophagy and loss of muscle mass in mice.[92]

In addition to these changes within the myofiber, muscle regenerative capacity is further hampered with age due to a reduction in—and impaired function of persisting—satellite cells.[93] As described earlier, quiescent satellite cells reside between the sarcolemma and basal lamina of myofibers and are critical for postnatal growth and regeneration following injury. Although the precise mechanism leading to their decline and dysfunction remains to be proved, evidence from other tissue- resident stem cell populations, including hematopoietic and neural stem cells, implicate chronic exposure to inflammatory factors and oxidative stress as likely factors underlying the disruption of the balance of stem cell proliferation, self-renewal, and appropriate differentiation.[94,95] Interestingly, despite the many indications of intrinsic defects in both myofibers and satellite cells with age, early work by Carlson and Faulkner[96] clearly demonstrated that the aged environment exerts a dominant effect on the regenerative capacity of muscle. In their study, the extensor digitorum longus (EDL) from young rats was transplanted into young or old rats, and vice versa. Surprisingly, the EDL from both young and old rats was able to regenerate to a similar extent in young recipients, whereas even young muscle regenerated poorly in the old recipients.[96] More recently, elegant experiments involving parabioses between young and old mice demonstrated a rejuvenation of satellite cell populations in aged mice when exposed to the youthful shared circulation.[97] These effects of the aged environment on muscle regenerative capacity have been shown to involve a decline in Notch signaling[98] and an increase in circulating Wnt molecules.[99]

Concomitant with the loss of muscle, aging also results in progressive bone loss, leading to bone fragility and increased risk for osteoporosis and fractures. In fact, age-related muscle wasting may coexist with osteoporosis, establishing a vicious cycle between dysfunctional muscle and bone. This age-related loss of bone results from a decreased capacity to effectively remodel itself. Osteoblast numbers and function decline with age[100] in association with decreased levels of sex steroids, GH, and IGF-1.[101–103] Interestingly, many of the same mechanisms that appear to impinge upon satellite cells with age also negatively affect the mesenchymal stem cells (MSCs) that give rise to osteoblasts, including oxidative stress.[104] Further, exposing MSCs from aged mice to a decellularized extracellular matrix produced by the MSCs of young mice corrected the proliferative and osteogenic differentiation defects in aged MSCs.[105] Unlike osteoblasts, osteoclast-mediated resorption remains constant, or even increases (by as much as 90% in postmenopausal women).[106] Ineffective remodeling of bone with advanced age is also partially explained by a reduction in responsiveness to mechanical loads,[107] possibly via alterations in mechanosensation by osteocytes.[14] Interestingly, this age-related decline in bone remodeling in response to mechanical load parallels that of the decreased muscle input, highlighting again, the possibility of a dominant role of muscle in the muscle-bone unit.

Body composition changes with aging also include the accumulation of fat viscerally, in the bone marrow, and infiltrating between and within muscle fibers.[108] The entity referred to as "sarcopenic obesity" is the co-occurrence of muscle loss with increases in adiposity, and it appears to be associated with functional disability.[109] There may be an underlying link between sarcopenic obesity and osteoporosis, because both muscle and bone exhibit increased numbers of adipocytes with age. Intramuscular fat has been shown be associated with inflammatory markers,[110] which may represent a mechanism explaining the recent observation that periaortic fat is associated with lower volumetric bone density of the adjacent spine.[111] Thus, the age-related decline in muscle mass and bone mass may be partly linked to adipocyte physiology and their proinflammatory milieu.

Emerging Endocrine Roles

A number of studies support the notion of muscle functioning in an endocrine fashion to affect other tissues and organs, including liver, pancreas, vasculature, fat, and importantly for our discussion, bone (reviewed by Pedersen and Febbraio[112]). These muscle-secreted endocrine factors, termed myokines, include myostatin, leukemia inhibitory factor (LIF), IL-6, IL-7, brain-derived neurotrophic factor (BDNF), IGF-1, FGF-2, follistatin-like protein 1 (FSTL-1), and irisin.[112] It is reasonable to postulate that many myokines could exert direct effects on adjacent—or even distant—bone, especially IGF-1 and FGF-2, given the primary importance of these factors in bone development.[15] Moreover, myokines could also indirectly impact bone through actions on other tissues. For example, IL- 6 can increase the secretion of insulin from the pancreas by increasing GLP-1 secretion from L cells and alpha cells.[113] Insulin could then feed into the recently described bone–pancreas endocrine loop and exert secondary effects upon bone.[3] Furthermore, the ability of muscle secreted irisin to induce brown-fat-like development of white fat[114] could also indirectly impact bone, given the crosstalk between bone and fat.[115,116] Additionally, the recent identification of a novel muscle secretory factor, musclin,[117] which is identical in protein sequence to bone-derived osteocrin,[118] suggests the possibility of an endocrine loop directly connecting muscle and bone.

Summary and Perspectives

Bone and muscle, from early embryonic development through aging and involution, are tightly coupled in both form and function. Numerous factors impact the relative mass of these two tissues, including genetic background, morphogens, sex steroids, other circulating factors (eg, GH and IGF-1), and mechanical forces. Although morphogens and genetic factors may primarily control muscle and bone development during embryogenesis, and sex steroids exert a dominant role during pubertal growth, it appears that mechanical forces exert an overarching control throughout life. In this regard, much of the data reviewed in this Perspective suggests that muscle predominates over bone in synchronizing tissue mass of the musculoskeletal system. That is not to say that communication between muscle and bone is necessarily unidirectional. As described in our discussion of the developmental biology of the musculoskeletal system, bone-derived Ihh is required for normal muscle development in mouse and chick embryogenesis. However, the postnatal setting clearly favors a strong influence of muscle on bone mass through mechanical signals, which likely employ the

actions of hormones and morphogens as determined by one's genetic background. Therapeutic approaches to treat age-related and disease-related musculoskeletal deficits based upon this “muscle-predominant” concept are an area of extremely active research, with many focused on targeting the myostatin/activin signaling pathway.[119–128] More recent data suggests that components of this pathway may also function directly in osteoblasts in a manner analogous to that of skeletal muscle,[129] and may represent a common molecular means by which bone and muscle coordinate their mass.

In the face of the wealth of evidence supporting a biomechanical link that coordinates bone and muscle mass, many important questions regarding the nature of this putative mechanism remain open. Are the responses to mechanical loading of bone and muscle occurring in parallel, or is muscle the primary responder to physical activity, transducing that signal to bone in a secondary fashion? What is the nature of the mechanical signal posited by the mechanostat theory?[130] Further, if osteocytes serve as the primary mechanosensor, how do they translate mechanical signals into the biochemical orchestration of bone remodeling? Does muscle function as a mechanical-endocrine converter, where the mechanical events experienced by muscle induce paracrine/endocrine effectors, which then influence bone development? This seems an ever more attractive hypothesis given evidence from the rapidly expanding myokine field and our growing understanding of organ system crosstalk in other physiologic contexts. Finally, many of the examples of postnatal coupling of bone and muscle cited in this Perspective are likely to involve some neurological input, given the well-described roles of the nervous system in regulating both normal muscle[61,62,131,132] and bone mass,[133–135] and may present an opportunity for unique therapeutic interventions. Answers to the questions above are critical for understanding the coordinate regulation of muscle and bone mass, and for identifying new targets to combat their inevitable decline with age.

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