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Review

Bone and skeletal muscle: Key players in mechanotransduction and potential overlapping mechanisms

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ABSTRACT

The development and maintenance of skeletal muscle and bone mass is critical for movement, health and issues associated with the quality of life. Skeletal muscle and bone mass are regulated by a variety of factors that include changes in mechanical loading. Moreover, bone mass is, in large part, regulated by muscle-derived mechanical forces and thus by changes in muscle mass/strength. A thorough understanding of the cellular mechanism(s) responsible for mechanotransduction in bone and skeletal muscle is essential for the development of effective exercise and pharmaceutical strategies aimed at increasing, and/or preventing the loss of, mass in these tissues. Thus, in this review we will attempt to summarize the current evidence for the major molecular mechanisms involved in mechanotransduction in skeletal muscle and bone. By examining the differences and similarities in mechanotransduction between these two tissues, it is hoped that this review will stimulate new insights and ideas for future research and promote collaboration between bone and muscle biologists.[1]

Contents

Abbreviations: AA, arachidonic acid; Akt, v-Akt Murine Thymoma Viral Oncogene; BAPTA-AM, 1,2-Bis(2-aminophenoxy)ethane-N,N,N′,N′-tetraacetic acid tetrakis(acetoxymethyl ester); CaMKKα, Ca^{2+}/calmodulin-dependent protein kinase kinase alpha; Cox, cyclooxygenase; DGK, diacylglycerol kinase; DGKζ, diacylglycerol kinase zeta; Dsh, Disheveled; ERK, extracellular signal-regulated kinase; FRB, FKBP12-rapamycin binding; FRET, fluorescence resonance energy transfer; Fzd, Frizzled; GAP, GTPase activating protein; Gd^{3+}, gadolinium; GDP, guanosine diphosphate; GPCR, G-protein coupled receptor; GSK3β, glycogen synthase kinase 3 beta; GTP, guanosine-5′-triphosphate; H_2O_2, hydrogen peroxide; IGF-1, insulin-like growth factor 1; iNOS, inducible nitric oxide synthase; LEF, lymphoid enhancer-binding factor; LEL, late endosomal/lysosomal; L-NAME, L-N^G-Nitroarginine methyl ester; LPAAT θ, lysophosphatidic acid acyltransferase theta; Lrp, lipoprotein receptor-related protein; MAPK, mitogen-activated protein kinase; MEK, Mitogen/Extracellular signal-regulated Kinase; MGF, mechano growth factor; mTOR, mechanistic or mammalian target of rapamycin; mTORC1, mTOR complex1; mTORC2, mTOR complex2; NO, nitric oxide; NOS, nitric oxide synthase; nNOS, neuronal nitric oxide synthase; Nox4, NADPH oxidase 4; O_2^-, superoxide; $ONOO^-$, peroxynitrite; p90RSK, 90 kDa ribosomal S6 kinase; PAPDL1, phospholipase; D1, phosphatidic acid; PG, prostaglandin; PI3K, phosphatidylinositide 3-kinase; Pkd, polycystic kidney disease; PTH1R, parathyroid hormone 1 receptor; RAF, rapidly accelerated fibrosarcoma; RANKL, receptor activator of nuclear factor kappa-B ligand; RAS, rat sarcoma oncogene; Rheb, Ras homologue enriched in the brain; RNS, reactive nitrogen species; ROS, reactive oxygen species; RUNX2, Runt-related transcription factor 2; SR, sarcoplasmic reticulum; SC, satellite cells; TCF, T-cell factor; Trp, transient receptor potential; TrpV1, transient receptor potential cation channel subfamily V1; TrpV4, transient receptor potential cation channel subfamily V4; TSC2, Tuberous Sclerosis Complex 2; Vps34, vacuolar protein sorting 34; Wnt, Wnt; Wingless, related integration site.

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Introduction

Skeletal muscle and bone play fundamental roles in human physiology, enabling locomotion and movement, enhancing blood flow to organs, and providing protection to vital organs, among others. Beyond the mechanical roles of these two organ systems, both are also major regulators of whole body metabolism. For instance, skeletal muscle serves as a storage site/consumer of amino acids and glucose, and secretes various myokines that affect metabolism in other tissues [1–3]. Bone serves as an ion bank for maintaining serum levels of physiologically crucial elements such as Ca^{2+} and Mg^{2+}, and also secretes active endocrine products [4–6]. In light of the far-reaching roles of these tissues in general health, it is imperative that the field comes to a better understanding of the conditions that concomitantly affect muscle and bone health, most notably reduced bone and/or skeletal muscle mass (either during pre/post-natal development or in adults). These conditions have the potential to increase the risk of injury and metabolic disease, reduce physical mobility, and ultimately affect the quality and duration of life.

Skeletal muscle mass and bone mass are regulated by a range of factors that include genetics, nutrition, hormones and growth factors and, in particular, mechanical stimuli [7,8]. It is well known that an increase in mechanical loading of skeletal muscle results in an increase in skeletal muscle mass (i.e., muscle hypertrophy), while a decrease in mechanical loading leads to a reduction of skeletal muscle mass (i.e., muscle atrophy) (for reviews see [9–11]). The mechanical loading experienced by skeletal muscle typically comprises the internal longitudinal and lateral forces, of varying magnitudes and velocities, which are generated by active muscle contractions (e.g., shortening, lengthening, or isometric contractions) or by passive stretch. Changes in mechanical loading are also known to play a major role in the regulation of bone mass and strength; increased mechanical loading at critical stages of growth and development result in increased bone mineral accrual, bone mass and strength, while reduced mechanical loading results in the loss of bone mass and strength (for reviews see [12–14]). Importantly, evidence suggests that the development and maintenance of bone mass is, in large part, dependent on skeletal muscle-derived mechanical loading [15,16].

Skeletal muscles contribute to the mechanical loading of bone in various ways that include the tensile forces developed by contracting muscles at their site of insertion, the compressive forces between bones developed by muscles contracting across joints, and bending forces experienced by long bones as muscles generate force for lifting distally held objects [15]. In support of a critical role for skeletal muscle-induced mechanical stimuli in the regulation of bone mass, studies have shown that a lack of muscle function in utero results in impaired fetal bone and joint development [17–21]. Furthermore, during postnatal skeletal growth (2–20 yr), there is a very strong positive correlation between muscle mass and bone mass, with gains in muscle mass preceding those in bone mass [22]. In fact, the associations between muscle/strength and bone mass in children are strong enough that clinical techniques for disease diagnosis can be founded upon them [23,24]. For instance, deficiencies in the amount of bone per unit muscle strength versus deficiencies in both factors allow for classification of diagnoses into primary (true or intrinsic) and secondary (physiologic) bone disorders. Combined, these data strongly suggest that greater forces, produced by larger muscles, may play a direct role in stimulating bone growth. Conversely, states of reduced muscle mass and function, such as various neuromuscular diseases (e.g. cerebral palsy and Duchenne muscular dystrophy [25,26]), spinal cord injury [27] and space flight [28], are all associated with a loss of bone mass. It is also interesting to note, and perhaps telling with respect to the influence of muscle forces on bone mass, that in many disease states, bone mass is typically not over adapted for muscle mass [29].

Despite the fundamental dependence on mechanical stimuli for the development and/or maintenance of bone and skeletal muscle mass, the exact mechanism(s) by which changes in mechanical loading are transduced into anabolic or catabolic signaling events (i.e., mechanotransduction) in these tissues remains to be fully determined. A thorough understanding of the cellular mechanism(s) responsible for mechanotransduction in bone and skeletal muscle is essential for the development of effective exercise and pharmaceutical strategies aimed at increasing, and/or preventing the loss of, mass in these critical tissues. Furthermore, it is clear that a sizeable and powerful complement of skeletal muscle and a robust and rigid skeleton are desirable outcomes for optimal connective tissue health. Therefore, it is worthwhile to understand the molecular underpinnings of mechanotransduction in both tissues and to determine whether both can be optimized in tandem [30]. Hence, the purpose of this review is to summarize our understanding of the key mechano-sensitive signaling events that are thought play a role in the regulation of bone and skeletal muscle mass. Importantly, we will also highlight important gaps in the body of knowledge in the hope that this will stimulate further research, and potentially collaboration between bone and muscle biologists.