Free Radical Biology and Medicine 98 (2016) 131–143

Contents lists available at ScienceDirect

Free Radical Biology and Medicine

journal homepage: www.elsevier.com/locate/freeradbiomed

Exercise-induced skeletal muscle signaling pathways and human athletic performance

Donny M. Camera [a], William J. Smiles [a], John A. Hawley [a,b,*]

[a] Centre for Exercise and Nutrition, Mary MacKillop Institute for Health Research, Australian Catholic University, Melbourne, Vic. 3065, Australia
[b] Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool L3 3AF, United Kingdom

ARTICLE INFO

Article history:
Received 9 November 2015
Received in revised form
28 January 2016
Accepted 3 February 2016
Available online 11 February 2016

Keywords:
Endurance exercise
Resistance exercise
Cell signaling
Molecular adaptation responses
Responder

ABSTRACT

Skeletal muscle is a highly malleable tissue capable of altering its phenotype in response to external stimuli including exercise. This response is determined by the mode, (endurance- versus resistance-based), volume, intensity and frequency of exercise performed with the magnitude of this response-adaptation the basis for enhanced physical work capacity. However, training-induced adaptations in skeletal muscle are variable and unpredictable between individuals. With the recent application of molecular techniques to exercise biology, there has been a greater understanding of the multiplicity and complexity of cellular networks involved in exercise responses. This review summarizes the molecular and cellular events mediating adaptation processes in skeletal muscle in response to exercise. We discuss established and novel cell signaling proteins mediating key physiological responses associated with enhanced exercise performance and the capacity for reactive oxygen and nitrogen species to modulate training adaptation responses. We also examine the molecular bases underpinning heterogeneous responses to resistance and endurance exercise and the dissociation between molecular 'markers' of training adaptation and subsequent exercise performance.

1. Introduction

The conversion of multiple signals generated during exercise to molecular events aimed at conserving cellular homeostasis and ultimately inducing phenotypic changes in skeletal muscle involves a cascade of events resulting in the activation and/or repression of specific signaling pathways regulating gene expression and protein synthesis/degradation [1–4]. One exercise-induced perturbation to cellular homeostasis is the increase in reactive oxygen (ROS) and nitrogen (RNS) species [5]. The generation of ROS and RNS products by the mitochondria and other subcellular compartments with exercise induce cellular damage and activates redox signaling pathways that can modulate the molecular mechanisms regulating protein synthesis and breakdown processes that ultimately form the basis for exercise training adaptations [5,6].

An important concept developed over the past decade is that the chronic responses to exercise training are likely to be the result of the acute, but cumulative effects of the responses to single exercise bouts [7]. As such, these acute and transient changes in gene transcription following a single exercise bout, when reinforced by repeated exercise stimuli, result in chronic effects on the rates of protein breakdown/synthesis that ultimately form the basis of skeletal muscle training adaptation and improvements in exercise capacity/performance [2,8]. Yet despite major breakthroughs in our understanding of how different exercise modalities activate specific cellular, molecular, and biochemical pathways, our understanding of how these effects exert their performance-enhancing benefit remains elusive. This is, perhaps, not surprising, given that exercise performance on any given day is ultimately the result of integrating multiple physiological, biomechanical and psychological factors simultaneously under a variety of different environmental conditions. Indeed, some of the variability observed in the physiological responses to standardized training protocols is likely to be underpinned by the multi-factorial and complex nature of the 'exercise response.' In this review we examine the molecular basis for exercise training-induced adaptations in skeletal muscle in response to both resistance- and endurance-based exercise including the roles of ROS and RNS on these cellular processes. We also examine the molecular bases underpinning these adaptations that may help explain the heterogeneous responses to exercise training, and the apparent dissociation between molecular 'markers' of training adaptation and subsequent exercise performance. The reader is also referred to several recent reviews published on these topics [2,3,9].

* Corresponding author at: Centre for Exercise and Nutrition, Mary MacKillop Institute for Health Research, Australian Catholic University, Melbourne, Vic. 3065, Australia.
E-mail address: john.hawley@acu.edu.au (J.A. Hawley).

http://dx.doi.org/10.1016/j.freeradbiomed.2016.02.007
0891-5849/

2. Molecular mechanisms mediating adaptation to resistance exercise

Mechanical overload of skeletal muscle promotes an increase in myofiber cross-sectional area, a process termed hypertrophy [10]. Resistance-based exercise (REX) provides the optimal "anabolic" signal to stimulate the protein synthetic response, with increases in muscle protein synthesis (MPS) and net myocellular protein accretion underlying the growth in individual muscle fibers and total muscle cross-sectional area [11]. REX elevates rates of MPS above basal levels for at least 24 h [12–15], but there is also a small rise in muscle protein breakdown [12]. Thus, any training-induced hypertrophic response requires a net accretion of contractile myofibrillar protein.

REX-induced increases in MPS are largely attributed to upregulation of protein translation initiation and control by the mechanistic target of rapamycin (mTOR) serine/threonine protein kinase [16]. mTOR exists in two multi-protein complexes (mTORC1 and mTORC2) with mTORC1 the predominant regulator of translation initiation. Two downstream substrates, ribosomal protein s6 (rps6) p70 kinase ($p70^{S6K}$) and eukaryotic initiation factor 4E (eIF4E)-binding protein 1 (4E-BP1) orchestrate a number of signals from mTORC1 (Fig. 1). $p70^{S6K}$ has several substrates that contribute to various steps of protein translation and has recently been implicated in the transcriptional regulation of ribosome biogenesis (i.e., to augment protein translational capacity) [17], whereas 4E-BP1 phosphorylation is thought to predominantly lead to the translation of 5′-tract of pyrimidine (5′-TOP) mRNAs that encode for translation factors and ribosomal proteins [18]. While some associations between $p70^{S6K}$ phosphorylation and acute post-REX MPS [19,20] and training-induced hypertrophy [21–24] exist, larger $p70^{S6K}$ phosphorylation responses have also been shown to parallel REX volume and/or lifting intensities [25–28] with the most pronounced effects in type II (fast-twitch) muscle fibers [29,30]. This latter point should not be dismissed, as a single bout of maximal eccentric contractions elicited a larger $p70^{S6K}$ phosphorylation than that provoked by maximal concentric efforts [31]. These findings may (a) reveal a potential molecular basis for the efficacy of eccentric-based REX training in promoting type II fiber hypertrophy [32] or (b) the higher force imposed by eccentric versus concentric work is merely a larger homeostatic perturbation within susceptible fibers (i.e., type II that rely heavily on fast glycolytic energy yield) and ultimately is inconsequential for chronic training adaptations [33,34]. In support for the latter

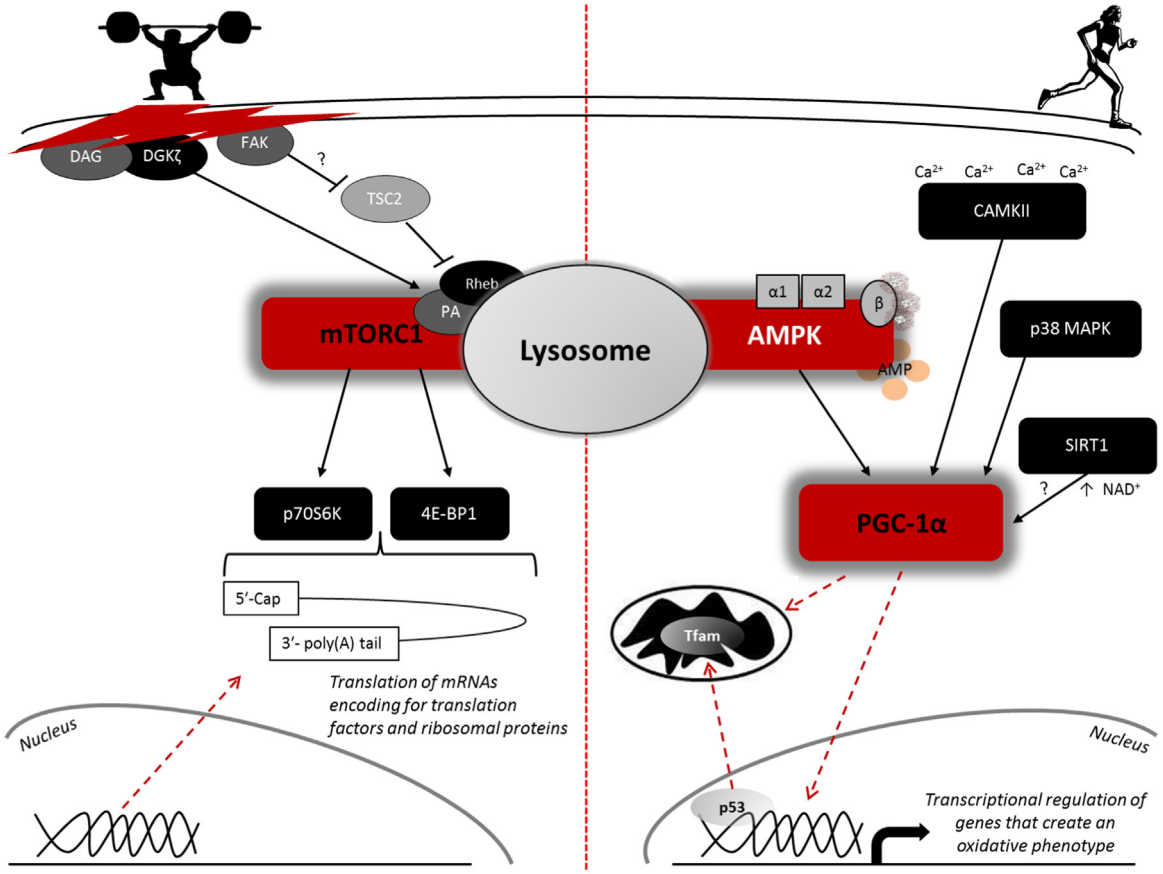

Fig. 1. Several signals propagated by resistance- and endurance-based exercise contraction converge on the lysosome. High-force resistance exercise (REX) contractions perturb transmembrane structures leading to the accumulation of membrane diacylglycerol (DAG), increased DAG kinase ζ (DGKζ) isoform activity and phosphatidic acid (PA) synthesis that, in turn, binds directly to mTORC1 in the same region as the inhibitory rapamycin-binding domain. In addition, REX triggers tuberin (or TSC2) removal from the lysosome enabling mTORC1 to interact with Ras homolog enriched in brain (Rheb), a small GTPase that is negatively regulated by TSC2. Sarcomeric adhesion-associated signaling molecules, such as focal adhesion kinase (FAK), may stimulate mTORC1 activity by similar mechanisms of TSC2-lysosomal abrogation. The collective outcome is an increase in cap-dependent mRNA translation and increases in cell size that is mitigated primarily by mTOR kinase substrates, p70 ribosomal protein s6 kinase ($p70^{S6K}$) and eIF4E binding protein 1 (4E-BP1). The endurance exercise (END)-evoked disruptions to cell homeostasis activates several protein kinases that seemingly "sense" the degree of stress imposed. For example, END triggers calcium (Ca^{2+}) oscillations to sustain locomotion (Ca^{2+}-dependent protein kinase II; CAMKII), causes glycogen and ATP depletion (AMP-dependent kinase; AMPK), elevates oxidative stress (p38 mitogen-activated kinase; p38 MAPK) and alters the reduction/oxidation state (sirtuin 1; SIRT1). These signals converge to post-translationally modify PPARγ-coactivator 1α (PGC-1α) which, in the compensatory defense of homeostasis, promotes an oxidative phenotype by coactivating numerous nuclear- and mitochondrial-encoded genes. Black arrows denote activation; straight black lines denote inhibition and dashed red arrows denotes translocation. Question marks refers to findings that are either equivocal or have not been confirmed *in vivo* skeletal muscle.