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Review

Regulation of muscle protein synthesis and the effects of catabolic states☆

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ABSTRACT

Protein synthesis and degradation are dynamically regulated processes that act in concert to control the accretion or loss of muscle mass. The present article focuses on the mechanisms involved in the impairment of protein synthesis that are associated with skeletal muscle atrophy. The vast majority of mechanisms known to regulate protein synthesis involve modulation of the initiation phase of mRNA translation, which comprises a series of reactions that result in the binding of initiator methionyl-tRNA$_i$ and mRNA to the 40S ribosomal subunit. The function of the proteins involved in both events has been shown to be repressed under atrophic conditions such as sepsis, cachexia, chronic kidney disease, sarcopenia, and disuse atrophy. The basis for the inhibition of protein synthesis under such conditions is likely to be multifactorial and includes insulin/insulin-like growth factor 1 resistance, pro-inflammatory cytokine expression, malnutrition, corticosteroids, and/or physical inactivity. The present article provides an overview of the existing literature regarding mechanisms and signaling pathways involved in the regulation of mRNA translation as they apply to skeletal muscle wasting, as well as the efficacy of potential clinical interventions such as nutrition and exercise in the maintenance of skeletal muscle protein synthesis under atrophic conditions.

This article is part of a Directed Issue entitled: Muscle wasting.

Contents

Abbreviations: 4E-BP1, eIF4E binding proteins; 5′-UTR, 5′-untranslated region; AMPK, AMP-activated protein kinase; eIF, eukaryotic initiation factor; GCN2, general-control nonderepressible; GEF, guanine nucleotide exchange factor; GSK-3, glycogen synthase kinase-3; HRI, heme-regulated inhibitor; ICU, intensive care unit; IGF-1, insulin-like growth factor-1; IRES, internal ribosome entry site; LPS, lipopolysaccharide; Met-tRNA$_i$, initiator methionyl-tRNA; mTORC1, mechanistic target of rapamycin in complex 1; NF-κB, nuclear factor kappa-B; p70S6K1, 70 kDa ribosomal protein S6 kinase 1; PDCD4, programmed cell death 4; PDK1, 3-phosphoinositol-dependent kinase 1; PERK, PKR-like endoplasmic reticulum-associated protein kinase; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PKR, double-stranded RNA-dependent protein kinase; REDD, regulated in DNA damage and development; Rheb, ras homolog enriched in brain; TSC, tuberous sclerosis complex; TNF, tumor necrosis factor; uORF, upstream open reading frame.

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1. Introduction

Protein synthesis and degradation are dynamically regulated processes that act in concert to control the accretion or loss of muscle mass. Muscle hypertrophy occurs when the rate of protein synthesis exceeds the rate of degradation, or, conversely, muscle atrophy occurs under conditions wherein the rate of protein synthesis is repressed relative to that of degradation. Thus, muscle atrophy can be caused by either a reduction in the rate of protein synthesis, a rise in the rate of degradation, or a simultaneous decline in synthesis in combination with an increase in degradation. Although protein degradation is undoubtedly an important contributor to the development and progression of muscle wasting under a variety of conditions, the focus of the present article will be on mechanisms involved in the impairment of protein synthesis associated with muscle atrophy in selected atrophic conditions, with the primary emphasis being on those conditions that are the focus of other articles in this issue of the journal.

2. mRNA translation

The process of mRNA translation occurs through a series of reactions that can be functionally divided into three phases: initiation, elongation, and termination (Hershey et al., 2012). The majority of mechanisms known to regulate mRNA translation involve the initiation phase, with many fewer occurring at elongation or termination (Hershey et al., 2012). Therefore, this review will focus primarily on modulation of translation initiation in muscle wasting.

2.1. The met-tRNA$_i$ binding step in translation initiation

One of the first steps in translation initiation involves formation of a ternary complex consisting of eukaryotic initiation factor (eIF) 2, GTP, and initiator methionyl-tRNA (Met-tRNA$_i$) (Hinnebusch and Lorsch, 2012). The ternary complex then associates with other initiation factors to form a multifactor complex that subsequently binds to the 40S ribosomal subunit to form the 43S preinitiation complex. During a later step in initiation, the GTP bound to eIF2 is hydrolyzed, and the eIF2·GDP complex is released from the preinitiation complex. The GDP bound to eIF2 must then be exchanged for GTP to permit formation of the ternary complex and efficient recycling of eIF2, because the affinity of Met-tRNA$_i$ for the eIF2·GDP complex is significantly lower compared to its affinity for eIF2·GTP. The GDP–GTP exchange on eIF2 is mediated by the heteropentameric complex, eIF2B. Interestingly, only one of the five eIF2B subunits (referred to as eIF2Bε) exhibits guanine nucleotide exchange activity, the remaining subunits are thought to act to modulate the activity of the complex (Reid et al., 2012).

2.2. The mRNA binding step in translation initiation

The binding of mRNA to the 43S preinitiation complex can occur through two functionally dissimilar mechanisms (Hinnebusch and Lorsch, 2012). In the first, eIF4E binds to the m^{7}GTP cap structure at the 5′-end of the mRNA, and the eIF4E·mRNA complex then interacts with eIF4G in association with eIF4A to form the eIF4F·mRNA complex. As part of the eIF4F complex, eIF4G subsequently interacts with eIF3 that is associated with the 43S pre-initiation complex to form the 48S pre-initiation complex. Thus, eIF4G acts as a molecular bridge linking the eIF4E·mRNA complex to the eIF3·40S ribosomal subunit complex. The 48S pre-initiation complex then scans along the 5′-untranslated region (5′-UTR) of the mRNA, and stops at the AUG start codon.

An alternative mechanism through which the 43S pre-initiation complex can bind to mRNA involves its association with mRNA at or near the AUG start codon in a cap-independent manner (Martínez-Salas et al., 2012). This interaction may require eIF4A and eIF4G, but does is independent of eIF4E. Many mRNAs that initiate translation through this mechanism have long, highly structured 5′-UTRs and contain a domain, referred to as an internal ribosome entry site (IRES), to which the 43S pre-initiation complex binds.

Regardless of whether association of the mRNA with the 43S pre-initiation complex occurs through a cap-dependent or -independent mechanism, the binding of the anti-codon loop of the Met-tRNA$_i$ to the AUG start codon of the mRNA halts the scanning of the 40S ribosomal subunit (Hinnebusch and Lorsch, 2012). The GTP bound to eIF2 is then hydrolyzed and the eIF2·GDP complex along with most of the other initiation factors are released from the 40S ribosomal subunit. The 60S ribosomal subunit then joins, and the resulting 80S initiation complex is competent to proceed with peptide chain elongation.

3. Regulatory mechanisms

3.1. Regulation involving eIF2 and eIF2B

One of the best-characterized mechanisms for regulating translation initiation involves the α-subunit of eIF2 (Wek et al., 2006). Phosphorylation of eIF2α on Ser51 indirectly inhibits translation initiation by transforming eIF2 from a substrate of the guanine nucleotide exchange factor (GEF) eIF2B, into a competitive inhibitor. Inhibition of eIF2B GEF activity by phosphorylated eIF2 results in accumulation of the eIF2·GDP complex that has limited affinity for Met-tRNA$_i$, leading to a decrease in the amount of the active Met-tRNA$_i$·eIF2·GTP complex available to participate in assembly of the 43S pre-initiation complex. Consequently, translation of most mRNAs is repressed under conditions that promote phosphorylation of eIF2α. Counterintuitively, the translation of some mRNAs is not repressed, but is instead enhanced in response to phosphorylation of eIF2α. Such mRNAs typically have multiple short upstream open reading frames (uORF) in the 5′-UTR that are required for enhanced translation when eIF2α is phosphorylated. A detailed discussion of the mechanism involved in this type of regulation is beyond the scope of this article, and the reader is referred to a recent review on this topic for further information (Wethmar et al., 2010).

Four kinases have been shown to phosphorylate eIF2α: double-stranded RNA-dependent protein kinase (PKR), PKR-like endoplasmic reticulum-associated protein kinase (PERK), general-control nonderepressible (GCN2), and heme-regulated inhibitor (HRI) (Wek et al., 2006). All four kinases phosphorylate eIF2α on Ser51, leading to inhibition of eIF2B activity, but are activated in response to diverse stresses. For example, PKR is activated by pro-inflammatory cytokines (Kang and Tang, 2012) and GCN2 is activated in response to deprivation of essential amino acids (Dever and Hinnebusch, 2005).

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