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Review

eIF3f: A central regulator of the antagonism atrophy/hypertrophy in skeletal muscle☆

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ABSTRACT

The eukaryotic initiation factor 3 subunit f (eIF3f) is one of the 13 subunits of the translation initiation factor complex eIF3 required for several steps in the initiation of mRNA translation. In skeletal muscle, recent studies have demonstrated that eIF3f plays a central role in skeletal muscle size maintenance. Accordingly, eIF3f overexpression results in hypertrophy through modulation of protein synthesis *via* the mTORC1 pathway. Importantly, eIF3f was described as a target of the E3 ubiquitin ligase MAFbx/atrogin-1 for proteasome-mediated breakdown under atrophic conditions. The biological importance of the MAFbx/atrogin-1-dependent targeting of eFI3f is highlighted by the finding that expression of an eIF3f mutant insensitive to MAFbx/atrogin-1 polyubiquitination is associated with enhanced protection against starvation-induced muscle atrophy. A better understanding of the precise role of this subunit should lead to the development of new therapeutic approaches to prevent or limit muscle wasting that prevails in numerous physiological and pathological states such as immobilization, aging, denervated conditions, neuromuscular diseases, AIDS, cancer, diabetes.

This article is part of a Directed Issue entitled: Molecular basis of muscle wasting.

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1. Introduction

Skeletal muscle mass represents approximately 40–50% of human body weight, making it the largest tissue mass and the major protein reservoir in the body. Maintenance of muscle mass is dependent on the balance between synthesis and breakdown of myofibrillar proteins (Attaix et al., 2012). Signal transduction pathways, which promote synthesis and/or degradation of muscle proteins, mediate the regulation of muscle homeostasis as well as muscle hypertrophy or atrophy. Hypertrophy is associated with growth in muscle mass, as a result of an increase in the size of pre-existing skeletal muscle fibers accompanied by incremented protein synthesis without apparent variation in the number of myofibers. In contrast, atrophy is characterized by an alteration in protein synthesis and an increased degradation of muscle proteins

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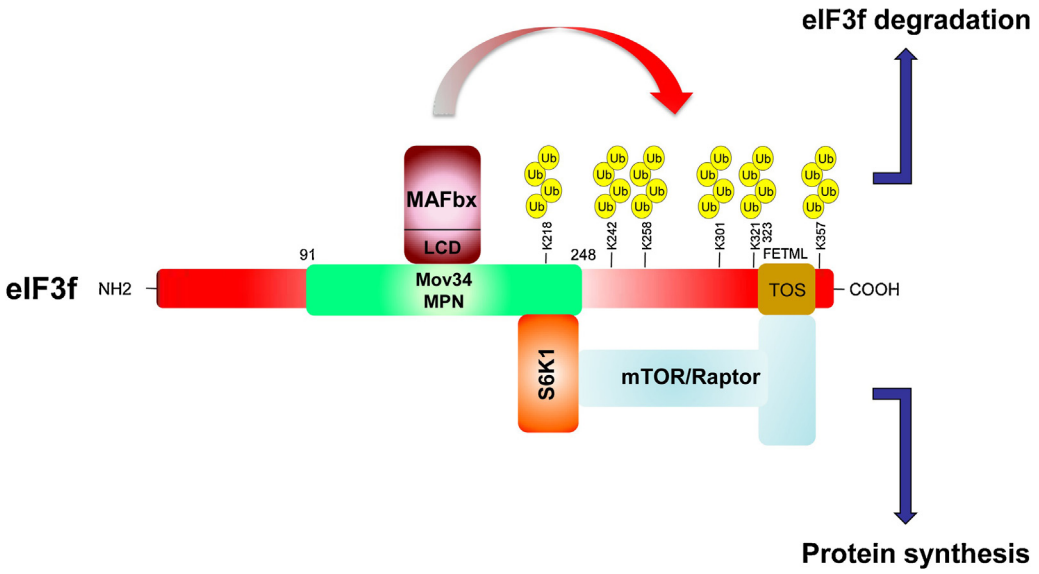

Fig. 1. Physical and functional links between eIF3f, mTOR-raptor, S6K1 and MAFbx/atrogin-1 in skeletal muscle. The leucine charged domain (LCD) of the ubiquitin ligase MAFbx/atrogin-1 physically interacts with the Mov34 domain of eIF3f and contributes to its ubiquitination in the C-terminal region and its subsequent degradation by the proteasome during muscle wasting. The Mov34 domain also interacts with the inactive hypophosphorylated form of S6K1. Under nutrient rich conditions, mTOR/raptor complex binds to the TOS motif of eIF3f and, thus can phosphorylate and activate S6K1. Active S6K1 is released from eIF3 complex leading to increased protein synthesis. In this model, eIF3f acts as a scaffolding protein allowing mTORC1-dependent activation of S6K1 upon insulin or growth hormone stimulation of muscle cells.

(Goldspink et al., 1986). Muscle atrophy that results in a state of weakness and emaciation of the body is the terminal phase of certain diseases or chronic infections such as cancer, AIDS, diabetes, bacterial infections and nerve degeneration. Muscle atrophy is also observed during aging, immobilization and trauma to the muscle.

The ubiquitin-proteasome system has been particularly involved in muscle atrophy after the discovery of the E3 ubiquitin ligases MAFbx/atrogin-1 (muscle atrophy F-box protein) and MuRF-1 (muscle RING finger-1), which are both overexpressed in various models of atrophy (fasting, cancer, diabetes, immobilization) (Bodine et al., 2001; Gomes et al., 2001). The knockout of genes coding for these factors confers resistance to certain types of atrophy, suggesting a major role of these E3 ligases in mediating muscle atrophy (Bodine et al., 2001). The function of E3 ubiquitin ligases is to ubiquitinate specific proteins to target them for recognition and degradation by the proteasome. MAFbx/atrogin-1 is responsible for the degradation of the transcription factor MyoD and the eukaryotic initiation factor of translation eIF3f. Therefore, MAFbx/atrogin-1 promotes muscle atrophy by inhibiting the transcription and translation of muscle genes, and prevents the replacement of degraded proteins (Lagirand-Cantaloube et al., 2009, 2008; Tintignac et al., 2005). In this review, we summarize the current state of knowledge concerning the central role of eIF3f in the control of skeletal muscle mass, particularly during muscle wasting.

2. Structure of eIF3f and its function in non-muscle cells

Mammalian eukaryotic initiation factor 3f (eIF3f, p-47) is one of the 13 subunits (designated eIF3a to eIF3m) of the eukaryotic initiation factor eIF3, a multi-protein complex required for the initiation of protein synthesis. eIF3 (800 kDa) is the largest and one of the most complex initiation factors known (Asano et al., 1997; Benne and Hershey, 1976). It is a multifunctional initiation factor that plays a major role in translation by operating at different levels of the initiation pathway; including the assembly of the ternary complex eIF2–GTP–Met-tRNA, binding of this complex and other components of the 43S PIC (preinitiation complex) to the 40S ribosomal subunit, mRNA recruitment to the 43S PIC, and scanning mRNA for AUG recognition. The eIF3f subunit is a member of the Mov34 family and contains a conserved (≈140-aa) domain named MPN (Mpr1/Pad1/N-terminal) (Fig. 1). This motif is found in two macromolecular complexes, homologous to eIF3, the COP9 signalosome, and the lid of 19S proteasome (Hofmann and Bucher, 1998). Moreover, both eIF3f and eIF3h interact directly with each other, supporting a possible scaffolding role for these subunits (Zhou et al., 2008).

The function of eIF3f within the eIF3 complex is not totally characterized. However, eIF3f is essential for *Schizosaccharomyces pombe* (*S. pombe*) viability, and its depletion markedly decreases the global protein synthesis in fission yeast (Zhou et al., 2005). The same effect on translation was described in cells infected with the severe acute respiratory syndrome coronaviruses and coronavirus infectious bronchitis virus (Xiao et al., 2008). Interestingly, eIF3f overexpression has been also associated with inhibition of HIV-1 replication (Valente et al., 2009). Furthermore, studies by Doldan et al. (2008a,b) showed that eIF3f is downregulated in several human tumors. The same group found that eIF3f overexpression in cancer cells negatively regulates cell growth by affecting the translation efficiency and the activation of apoptosis (Shi et al., 2006). Moreover, caspase-processed isoform of the cell division kinase 11 ($Cdk11^{p46}$) binds and phosphorylates eIF3f at Ser-46 and Thr-119 during apoptosis in A375 melanoma cells, leading to an inhibition of translation (Shi et al., 2003). In a recent study, Wen et al. (2012) reported that eIF3f exhibited a tumor suppressive function in pancreatic cancer. Mechanistically, the authors found that eIF3f inhibits both cap-dependent and cap-independent translation and that eIF3f promotes rRNA degradation through direct interaction with heterogeneous nuclear ribonucleoprotein K (Wen et al., 2012). From these data, it appears that eIF3f can act in different ways according to cellular contexts. Thus, this protein is essential for *S. pombe* viability but in cancer cells, it is a negative regulator of cell growth and protein translation, and it plays a central role in apoptotic signaling (Marchione et al., 2013).

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