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Review article

Interactions of the super complexes: When mTORC1 meets the proteasome

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ABSTRACT

Homeostatic regulation of energy and metabolic status requires that anabolic and catabolic signaling pathways be precisely regulated and coordinated. Mammalian/mechanistic target of rapamycin complex 1 (mTORC1) is a mega protein complex that promotes energy-consuming anabolic processes of protein and nucleic acid synthesis as well lipogenesis in times of energy and nutrient abundance. However, it is best characterized as the regulator of steps leading to protein synthesis. The ubiquitin-proteasome proteolytic system (UPS) is a major intracellular proteolytic system whose activity is increased during periods of nutrient scarcity and in muscle wasting conditions such as cachexia. Recent studies have examined the impact of mTORC1 on levels and functions of the 26S proteasome, the mega protease complex of the UPS. Here we first briefly review current understanding of the regulation of mTORC1, the UPS, and the 26S proteasome complex. We then review evidence of the effect of each complex on the abundance and functions of the other. Given the fact that drugs that inhibit either complex are either in clinical trials or are approved for treatment of cancer, a muscle wasting condition, we identify studying the effect of combinatory mTORC1-proteasome inhibition on skeletal muscle mass and health as a critical area requiring investigation.

1. Introduction

Regulation of cellular nutrient and energy homeostasis demands that pathways that promote anabolism and catabolism are usually antagonistically controlled. As such, in conditions of low energy status, catabolic pathways of glycogenolysis/glycolysis, lipolysis and beta-oxidation of fatty acids, and proteolysis predominate over the anabolic pathways of glycogenesis, lipogenesis, and protein synthesis (Fig. 1). This happens even though pyruvate, acetyl CoA and amino acids, the products of the catabolic pathways, are substrates that can be used for the afore-mentioned anabolic processes.

Synthesis of glycogen and triacylglycerol (quantitatively the most important complex carbohydrate and lipid in mammals) starts with glucose (Roach et al., 2012), fatty acids and glycerol (Czech et al.,

Abbreviations: 4E-BP1, eukaryotic mRNA translation initiation factor 4E binding protein 1; 19S, 19S regulatory particle, a sub-complex of 26S proteasome; AA, amino acid; AMPK, AMP-dependent kinase; βTrCP, beta-transducin repeat containing E3 ubiquitin protein ligase (an F-box containing protein that functions as a substrate-recognition subunit of SCF type ubiquitin protein ligase); CASTOR 1, cellular arginine sensing for mTORC1; CHOP, C/EBP homologous protein; DEPTOR DEP domain containing mTOR-interacting proteinE1, ubiquitin activating; E2, ubiquitin conjugating; E3, ubiquitin protein ligase; ERAD, endoplasmic reticulum-associated degradation; GATOR 1/2, GAP activity towards Rags complex 1/2; GRP, glucose-regulated protein 78; Huwe1, HECT, UBA And WWE domain containing E3 ubiquitin protein ligase; IRS, insulin receptor substrate; KICSTOR, KPTN, ITFG2, C12orf66, and SZT2-containing regulator of mTORC1; MAFbx, muscle atrophy F-box/atrogin-1; MLST8, mammalian lethal with SEC13 protein 8; mTORC1, mammalain/mechanistic target of rapamycin complex 1; MuRF1, muscle RING finger 1; MUSA1, muscle ubiquitin ligase of the SCF complex in atrophy-1; NRF 1, nuclear respiratory factor 1; PDCD4, programmed cell death 4; PERK, PKR-like endoplasmic reticulum kinase; PRAS40, proline-rich AKT substrate of 40 kDa; PTM, post translational modification; Rag, Rag GTPases; RAPTOR, regulatory associated protein of mTORC1; REDD1, regulated in development and DNA damage 1; Rheb, Ras homolog enriched in brain; Rnf181, ring finger protein 181; Rpn, proteasome regulatory particle non-ATPase; Rpt3, proteasome regulatory particle triple-A ATPase 3; S6K1, ribosomal protein S6 kinase 1; SAMTOR, S-adenosylmethionine sensor upstream of mTORC1; SCF, a ubiquitin protein ligase complex consisting of Skp1, Cullin, a RING finger protein Rbx1/Roc1, and an F-box containing protein; SLC38A9, solute carrier family 38 member 9; TSC, tuberous sclerosis complex; Ube3a, ubiquitin protein ligase E3A; Ube3c, ubiquitin protein ligase E3C; Ubr4, ubiquitin protein ligase E3 component n-recognin 4; UPS, ubiquitin-proteasome proteolytic system; USP19, ubiquitin-specific protease-19; WIPI 2, WD Repeat Domain, Phosphoinositide Interacting 2; XBP-1s, spliced form of X-box binding protein 1

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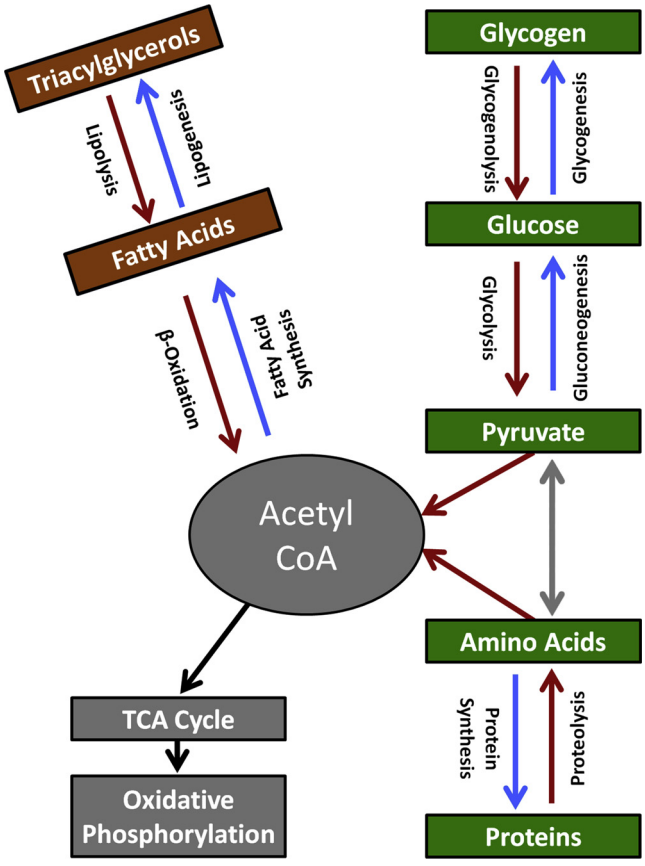

Fig. 1. Interrelationships amongst the pathways of carbohydrate, lipid and protein anabolism and catabolism. In conditions of nutrient abundance, the anabolic pathways (blue arrows) will predominate over the catabolic pathways (red arrows) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

2013), and proceeds along well described pathways. In comparison, there are 20 different canonical protein amino acids that can be assembled in various orders to form polypeptides (proteins) of diverse chain lengths. As such, regulation of protein synthesis is much more complex compared to the synthesis of glycogen and triacylglycerol.

The growth factor- and nutrient-sensitive mammalian/mechanistic target of rapamycin complex 1 (mTORC1) is a master regulator of macromolecule synthesis and anabolism (reviewed in (Ben-Sahra and Manning, 2017; Eltschinger and Loewith, 2016; Saxton and Sabatini, 2017). Although mTORC1 can promote lipogenesis (A. Caron et al., 2015) and nucleic acid synthesis (Iadevaia et al., 2014; Kimoloi, 2018), it is best understood as a positive regulator of mRNA translation and protein synthesis (Eltschinger and Loewith, 2016). The protein mass of a cell or tissue is the net balance between the processes of protein synthesis and proteolysis. In this regard, mTORC1 can also regulate autophagy, one of the pathways of proteolysis (see below). These functions underline the significance of the complex in regulating tissue protein mass.

Compared to the catabolism of the other macromolecules, the mechanisms of intracellular proteolysis are much more complex. For example, glycogenolysis is initiated by glycogen phosphorylase, and lipolysis by a limited number of well-defined lipases. On the other hand, intracellular proteolysis can be triggered by the activation of at least three catabolic pathways: the ubiquitin-proteasome proteolytic system (UPS), the autophagy/lysosomal proteolytic system, and the Ca-dependent proteases (calpains). Each of the pathways has layered points of regulation, a point that is particularly evident for the ubiquitin-dependent proteolytic pathway (see below). In tissues like skeletal muscle, activation of each of these proteolytic pathways can be triggered by diverse factors, including nutrient deprivation, infection, denervation and muscle disuse. Although any combination of the three proteolytic pathways may be activated depending on the triggering factors, the autophagy/lysosomal pathway and UPS are the pathways responsible for the bulk of proteolysis in skeletal muscle (Mammucari et al., 2007; Sandri et al., 2004; *J* Zhao et al., 2007; *J* Zhao et al., 2008). The latter system, the UPS, is characterized by extensive layers of regulation in terms of substrate targeting, selectivity (and de-selectivity, for example via de-ubiquitination; see section 3 below), and proteolytic cleavage of the substrates. This pathway is also the main intracellular proteolytic pathway that is critical to the regulation of skeletal muscle mass (Collins and Goldberg, 2017; Kornitzer and Ciechanover, 2000) and whose elevated activity is linked to excessive muscle wasting seen in cancer cachexia (Hoeller and Dikic, 2009; Orlowski and Kuhn, 2008) and sarcopenia (Altun et al., 2010; Lydie Combaret et al., 2009).

Although mTOR can form at least two complexes (mTORC1 and 2) with some distinct subunits and unique functions, and although mTORC2, via its activation of AKT (Hresko and Mueckler, 2005; Sarbassov et al., 2005) and suppression of TSC2 (Inoki et al., 2002), is required for full mTORC1 activation, it is mTORC1 that is better understood for its regulation of synthesis of protein and other macromolecules. As mentioned above, regulation of protein synthesis and proteolysis, processes that can account for greater than 25% of energy expenditure in mammals (Rolfe and Brown, 2017), is quite complex. For these reasons, this review will focus on the link between mTORC1, the principal regulator of protein synthesis, and the 26S proteasome, a principal mediator of proteolysis.

While the link between mTORC1 and suppression of autophagy has been long established, until recently, much less is known about the link between mTORC1 and the UPS. In this review we first summarize recent findings on the regulation of mTORC1 and the ubiquitin-dependent proteolytic system, with specific focus on the 26S proteasome. We then review current evidence for the regulation of the 26S proteasome by mTORC1, and vice versa. Because of the significance of skeletal muscle in whole body protein metabolism, we emphasize available studies in this tissue.

2. Regulation of mTORC1 functions

In addition to the mTOR protein itself, which nucleates the complex and is responsible for its kinase activity, mTORC1 also consists of the substrate adaptor protein raptor (regulatory-associated protein of mTOR), MLST8 (mammalian lethal with SEC13 protein 8), PRAS40 (proline-rich AKT substrate of 40 kDa) and the negative regulator DEPTOR (DEP domain containing mTOR-interacting protein) (reviewed in (Saxton and Sabatini, 2017), Fig. 2). In skeletal muscle, mTORC1 is activated in conditions of abundance of nutrient/substrates (including amino acids (Hara et al., 1998; Reynolds IV, Bodine, and Lawrence, 2002), glucose (Tzatsos and Kandror, 2005), fatty acids (Rivas et al., 2009), anabolic hormones like insulin/IGF-1 (Inoki et al., 2002; Tee et al., 2003), energy (Gwinn et al., 2008; Inoki et al., 2003a), and oxygen (Arsham et al., 2003), reviewed in (André and Cota, 2012; Harris and Lawrence, 2003; Kim and Guan, 2019; Saxton and Sabatini, 2017)). It can also be activated by mechanical stress (Reynolds IV et al., 2002). However, it is the mechanisms involved in the activation of the complex by amino acids and insulin/IGF-1 that have received the greatest attention. Initiation of insulin/IGF-1 signaling leads to the activation of AKT/protein kinase B which phosphorylates and inhibits TSC1/2 (tuberous sclerosis complex 1/2), an inhibitor of Rheb (Ras homolog enriched in brain). Inhibition of TSC1/2 complex leads to the formation of GTP-bound Rheb and its localization to the lysosomal membrane, where it activates mTORC1 (for recent detailed reviews, see (Ben-Sahra and Manning, 2017; Saxton and Sabatini, 2017)).

Although mTORC1 signaling is activated in response to treatment with either insulin or IGF-1, under normal physiological settings,

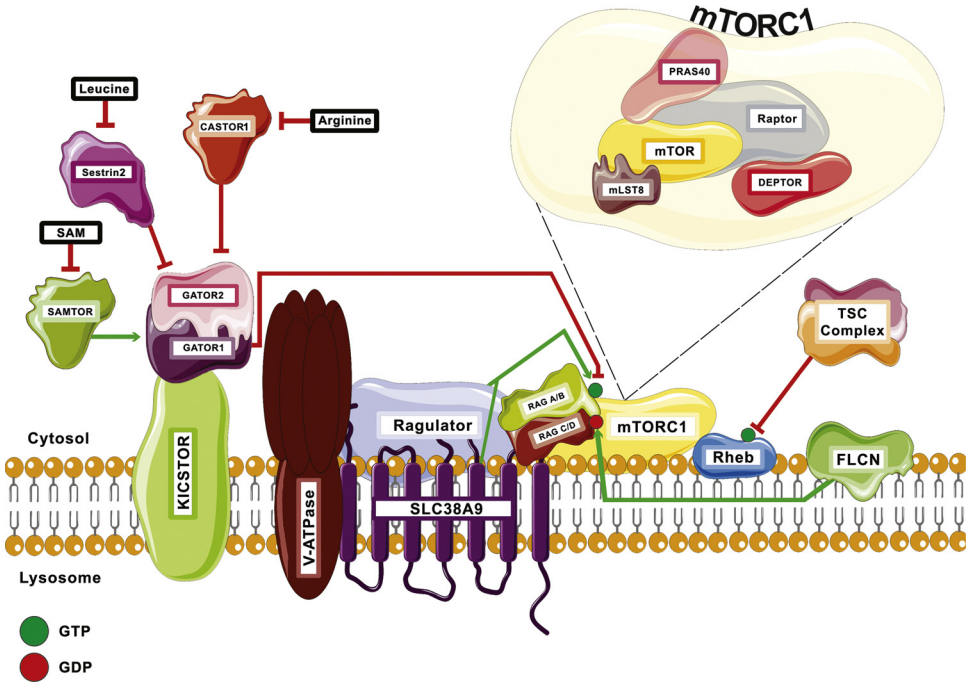

Fig. 2. mTORC1 and its activation. CASTOR1/2 and Sestrin2 respectively mediate arginine and leucine sensing by mTORC1 via their interactions with GATOR2, a protein complex that inhibits the mTORC1 inhibitor, GATOR1. SAMTOR on the other hand mediates methionine sensing by mTORC1 via its interaction with GATOR1. In the presence of the relevant amino acids (AA), the interactions of CASTOR1/2 and Sestrin2 with GATOR2, and that of SAMTOR and GATOR1 are disrupted. As a result, mTORC1 is activated. Insulin/IGF-1 activation of mTORC1 (not shown) is ultimately relayed via AKT-catalyzed phosphorylation of TSC2, an event that ensures that the mTORC1 activator Rheb is in its GTP-loaded state. GATOR1, tethered to the lysosome via KICSTOR, inhibits Rag A/B by converting the Rag protein from GTP to GDP-loaded form. v-ATPase and the amino acid transporter SLC38A9 too are involved in relaying AA availability to the activation of mTORC1. Rag A/B complexed with Rag C/D, along with the Ragulator, facilitates AA-induced mTORC1 localization to the lysosome. Folliculin-FNIP2 (denoted by FLCN) is a GTPase that, in response to AA availability, keeps Rag C/D in the GDP-bound form thus activating mTORC1.

increased levels of these hormones are a readout of organismic substrate/energy status. In fact, of all the upstream activators of mTORC1, much more is understood about the mechanism of activation of the complex by amino acids, especially the branched-chain amino acid leucine, the basic amino acid arginine, the amide-containing amino acid glutamine and the sulphur-containing amino acid methionine (Kim and Guan, 2019; Wolfson and Sabatini, 2017). Several mechanisms involved in mTORC1 activation by leucine and other amino acids have been described (reviewed in (Adegoke et al., 2012; André and Cota, 2012; Kim and Guan, 2019)) (Fig. 2). The best understood of these involves the Rag GTPases. In this model, GTP loaded RagA or B forms a complex with GDP-loaded RagC or D and, along with the Ragulator complex, recruits mTORC1 to the lysosomal membrane where insulin/IGF-1 activated Rheb is located. GATOR 2 (GAP activity towards Rags complex 2), via its interactions with CASTOR 1 (cellular arginine sensing for mTORC1) and Sestrin 2 (for leucine sensing), mediates arginine and leucine sensing by mTORC1 (reviewed in (Saxton and Sabatini, 2017). GATOR 1 complex, an inhibitor of mTORC1, interacts with SAMTOR (S-adenosylmethionine sensor upstream of mTORC1), itself a protein that interacts with the methionine metabolite S-adenosylmethionine (SAM) and therefore relays methionine availability to mTORC1 (Gu et al., 2017) (Fig. 2).

Amino acid-induced localization of mTORC1 to the lysosome, close to Rheb, leads to the activation of the complex. Raptor-bound substrates are then phosphorylated by the activated mTORC1 (Saxton and Sabatini, 2017)). Amongst such substrates, ribosomal protein S6 kinase 1 (S6K1) and eukaryotic translation initiation factor 4E binding protein 1 (eIF4E-BP1 or 4E-BP1) are the most widely studied. Details of mechanisms of activation of mTORC1 by amino acids are much more complex than are described here, and are an area of active research. Readers are referred to recent more detailed reviews of the subject (Ben-Sahra and Manning, 2017; Kim and Guan, 2019; Wolfson and Sabatini, 2017). Although many of the initial discoveries in the regulation of mTORC1 were made in non-mammalian/immortalized cell lines, many of the components of the complex and their regulation by nutrients and/or exercise and/or catabolic factors have been demonstrated in mammalian skeletal muscle by us (for example, see (Adegoke et al., 2009; Kakade et al., 2014; Kimball, Shantz, Horetsky, and Jefferson, 1999; Xu et al., 2019; Zargar et al., 2011) and others (for example, (Bentzinger et al., 2008; Bodine et al., 2001a,b; Graber et al., 2019; Reynolds, Reid, Larkin, and Dengel, 2004; Risson et al., 2009; Z. Song et al., 2017).

Since mTORC1 is activated in conditions of abundance of nutrients/energy/oxygen, mechanisms must exist to turn off the complex when those are lacking. Upstream signals that suppress mTORC1 include AMP-dependent kinase (AMPK), which phosphorylates and activates TSC1/2 and therefore promotes the conversion of Rheb to its GDP-bound, inactive form. As such, Rheb cannot activate mTORC1 (Inoki et al., 2003b). Regulated in development and DNA damage 1 (REDD1, also called RTP801) is another negative regulator of mTORC1. Initially described as mediating hypoxia- (Brugarolas et al., 2004) and energy stress- (Sofer et al., 2005) induced suppression of the complex, we have shown that in skeletal muscle/L6 myotubes, REDD1 acts via TSC1/2 complex to mediate dexamethasone-induced suppression of mTORC1 (H. Wang et al., 2006). Moreover, in mice lacking REDD1, muscle overload-induced increase in mTORC1 signaling and muscle mass are augmented (Gordon et al., 2016a,b) while sepsis- or glucocorticoid-induced decrease in mTORC1 signaling and reduced muscle protein synthesis are attenuated (reviewed in (Gordon et al., 2016a,b)).

3. Regulation of the ubiquitin-proteasome proteolytic pathway

Unlike mTORC1, the UPS in skeletal muscle is usually activated under nutrient deficiency/atrophy conditions such as starvation, elevated blood levels of glucocorticoids, inflammation, and other catabolic environments like cancer and infection (Bilodeau, Coyne, and Wing, 2016; Sue C. Bodine and Baehr, 2014).

With a few exceptions (Finley, 2009), proteins to be degraded by this pathway are first conjugated to > 4 units of ubiquitin via an ATP-dependent cascade of reactions catalyzed by the sequential activities of ubiquitin activating (E1), conjugating (E2) and protein ligase (E3) enzymes (Fig. 3a,b). Ubiquitinated proteins are then delivered to the multi-subunit mega protein complex, the 26S proteasome, within which the actual proteolysis occurs. However, it is at the level of protein ubiquitination that specificity of protein degradation is conferred. This is facilitated by the hierarchical organization of the enzymes involved in ubiquitination. Whereas there is only one major E1 enzyme that activates ubiquitin (Haas and Siepmann, 2018), activated ubiquitin is

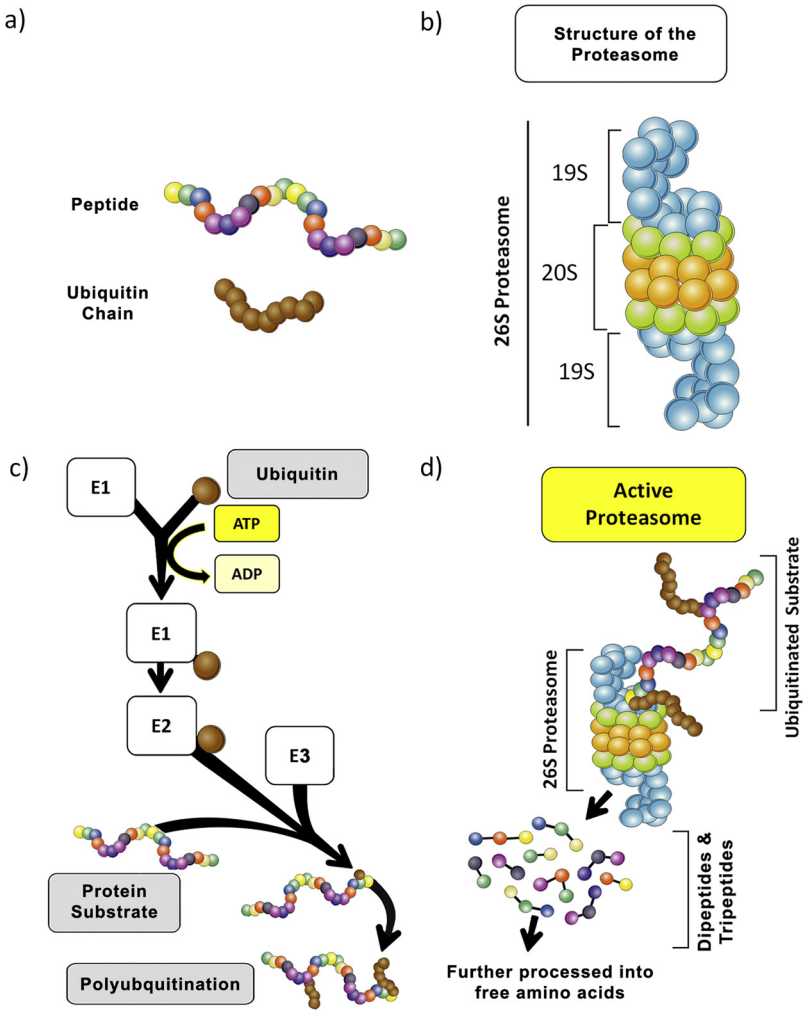

Fig. 3. Ubiquitin proteolytic system. A) Protein substrate and a ubiquitin chain are shown. B) Ubiquitin conjugation. C) 26S proteasome and D). Degradation of ubiquitinated protein into small peptides that are subsequently cleaved to free amino acids.

funneled to myriads of ubiquitin conjugating enzymes (E2). Although a few E2 enzymes may catalyze transfer of ubiquitin to substrates, in most cases, the E2s funnel the ubiquitin to an even wider array of ubiquitin protein ligases (E3). Some of the E3s function as monomeric enzymes whereas a wider group, including cullin-RING ligases, functions in the context of ligase complexes (reviewed in (Zheng and Shabek, 2017). Interestingly, many members of the latter group of ligases recognize their substrates only after they have been phosphorylated. This requirement not only introduces another level of selectivity, but also suggests a potential point of interactions between mTORC1 and UPS. The E3 ultimately facilitates the transfer of ubiquitin to substrates by E2 or directly catalyzes the formation of (usually) an isopeptide bond between the carboxyl terminus of ubiquitin and ε-amino group of a lysine residue in the substrate. Interestingly, a number of E3s, including atrogin-1/muscle atrophy F-box (MAFbx) (Bodine et al., 2001a,b; Gomes et al., 2001), muscle RING finger 1 (MuRF1) (Bodine et al., 2001a,b) and muscle ubiquitin ligase of the SCF complex in atrophy-1 (MUSA1) (Sartori et al., 2013) are either exclusively expressed or enriched in muscles.

Much like the phosphatases can reverse the actions of kinases, a group of enzymes called deubiquitinating enzymes can undo ubiquitin conjugation. These enzymes remove ubiquitin from substrates previously ubiquitinated, either to salvage ubiquitin as substrates are degraded, or pre-proteolysis to correct ubiquitination errors and therefore prevent proteins from being degraded inadvertently. This represents another level of control of the UPS. We previously identified and characterized a deubiquitinating enzyme, ubiquitin specific protease 19 (USP 19), whose level in skeletal muscle is elevated in catabolic states, including starvation, treatment with dexamethasone, and tumor implantation (L Combaret et al., 2005). This enzyme regulates cell proliferation and its depletion leads to increased abundance of myofibrillar proteins. Significantly, in USP19 knock out mice, muscle loss in response to diverse catabolic stimuli is significantly attenuated (reviewed in (Simon S. Wing, 2016)).

As mentioned before, about 4 ubiquitin units, within a single chain, need to be attached, via an isopeptide linkage between the carboxyl terminus of the incoming ubiquitin and lysine 48 of the preceding (accepting) ubiquitin. Ubiquitinated proteins are then recognized and threaded through the core of the barrel shaped proteolysis complex, the 26S proteasome, where substrates are degraded (Fig. 3c, d). The lysine 48-linked chain is only one of myriads of polyubiquitin chains that can be formed. These diverse polyubiquitin chains allow ubiquitination to be used to target proteins for purposes other than degradation, including regulation of functions and localization to specific sites within the cell. Further details on types, mechanisms and functions of ubiquitination are available in recent reviews (for example, (Kwon and Ciechanover, 2017; Swatek and Komander, 2016; Zheng and Shabek, 2017)).

The 26S proteasome is a multi-subunit mega complex with a mass of ~2.5 MDa. It is an assembly of two sub complexes, the 19S cap and 20S proteasome (also referred to as 19S particle or regulatory particle and 20S particle or core particle, respectively; reviewed in (Collins and

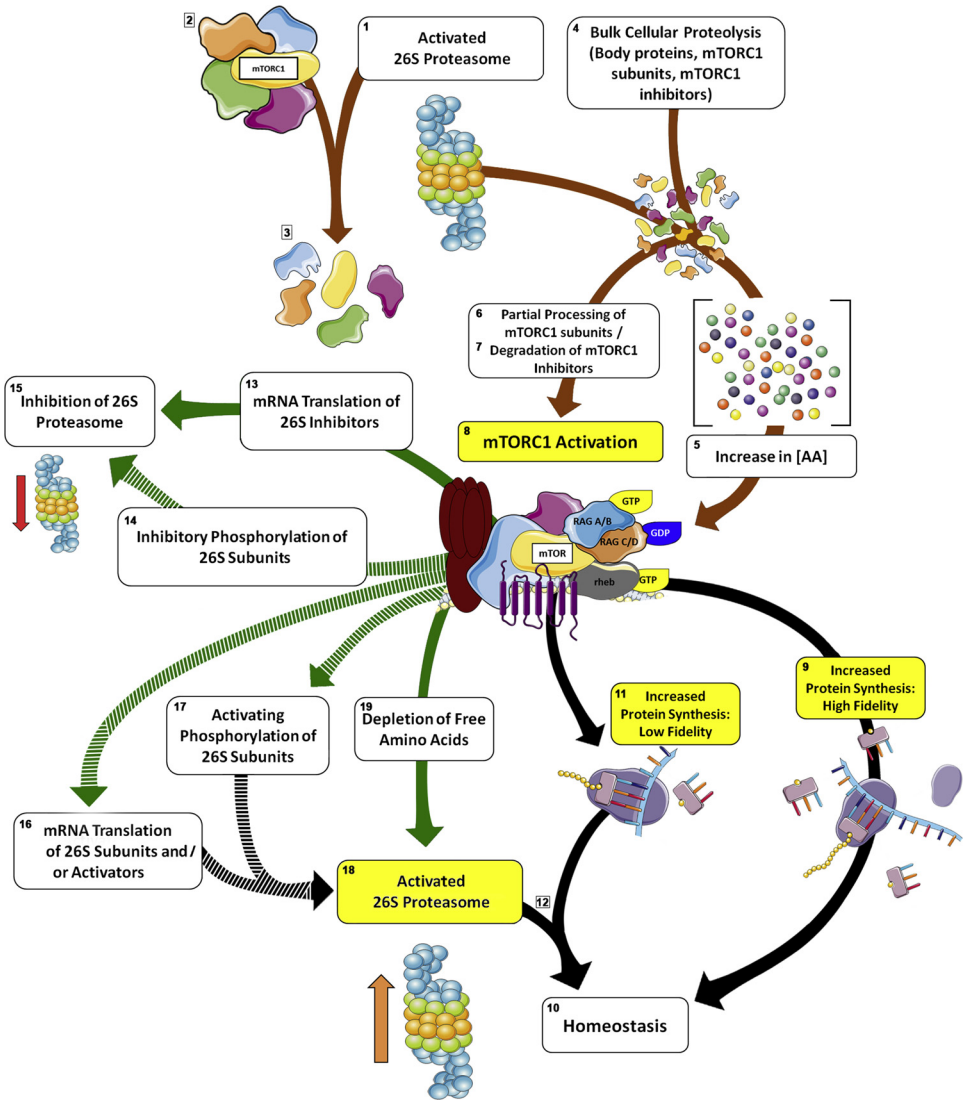

Fig. 4. Possible interactions between mTORC1 and 26S proteasome.
Activated 26S Proteasome (**1**) can degrade mTORC1 components (**2**) leading to disassembled mTORC1 (**3**). Activated 26S Proteasome can also degrade bulk cellular proteins (**4**) leading to increased free AA (5) that can promote mTORC1 assembly and activation (**8**). The proteasome can also catalyze partial proteolysis of an mTORC1 subunit (**6**), or degrade an mTORC1 inhibitor, e.g. DEPTOR (**7**), which in either case would lead to mTORC1 activation (**8**). Activated mTORC1 can stimulate bulk cellular mRNA translation: if the increased protein synthesis occurs with high fidelity (**9**), cellular homeostasis is maintained (**10**); if, however, the mTORC1-induced increase in protein synthesis comes at the expense of fidelity (**11**), the 26S proteasome may be activated to degrade misfolded/truncated proteins (**12**) and thus restore homeostasis (**10**). Activated mTORC1 can also stimulate the translation of an mRNA encoding a proteasome inhibitor (**13**), or negatively phosphorylate (inhibitory phosphorylation) a proteasomal subunit (**14**), in either case leading to inhibition of proteasome assembly and function (**15**). On the other hand, activated mTORC1 can stimulate the synthesis of proteasomal subunits (**16**), or positively phosphorylate (activating phosphorylation) a proteasomal subunit (**17**), in either case leading to activation of proteasome assembly and function (**18**). Activated mTORC1 may also lead to amino acid (AA) depletion ((**19**), as a result of the AA being used to make proteins). This amino acid depletion, especially of an AA like leucine, can activate 26S function (**18**) in order to degrade cellular proteins and raise intracellular free AA levels. In the figure, broken arrows indicate theoretical interactions for which experimental confirmations are needed.

Goldberg, 2017; Finley et al., 2016; Wehmer and Sakata, 2016). The 28-subunit 20S proteasome consists of 14 α and 14 β subunits arranged as a $\alpha_7\beta_7\beta_7\alpha_7$ cylindrical complex, within which actual proteolysis occurs, and is abutted at one or both ends by 19S caps (Fig. 3c). This 19S regulatory particle in turn consists of two sub complexes, referred to as the lid and the base, each of which is made up of nine subunits. Amongst the subunits of the lid are deubiquitinating enzymes. In addition, a number of ubiquitin protein ligases, including Ube3a, Ube3c, Rnf181, Huwe1, and Ubr4, too associate with the proteasome (Besche et al., 2014). Other subunits of the 19S recognize and therefore facilitate the binding of ubiquitinated proteins to the proteasome. These include Rpn1, Rpn10 and Rpn13 (Collins and Goldberg, 2017; Y. Y. Shi et al., 2016). In addition to these intrinsic proteasomal ubiquitin receptors, there are shuttle ubiquitin receptors, including Rad 23, Dsk2, and Ddi1, that can bind to both ubiquitinated proteins and the proteasome, thus facilitating the delivery of the former to the latter (Collins and Goldberg, 2017; Finley et al., 2016). Finally, 6 subunits of the base component of the 19S proteasome belong to the AAA class of ATPases. These function to generate energy required to unwind substrates as they are threaded through the junction between the base of the 19S cap and the 20S proteasome (Finley et al., 2016). Much more can be said about the subunit and functional complexities of the 26S proteasome, however this abridged review suffices to highlight the architectural and functional organization of the complex, along with potential for regulation of the functions of the complex by multiple factors. Readers are referred to recent excellent reviews on the subject (Budenholzer et al., 2017; Collins and Goldberg, 2017; Finley et al., 2016).

Many components of the UPS and their regulation by nutrients and/or exercise and/or catabolic factors have been demonstrated in skeletal muscle by us (for example, see (Adegoke et al., 2009; L. Combaret et al., 2005; Medina, Wing, and Goldberg, 1995; Medina, Wing, Haas, and Goldberg, 1991; S. S. Wing and Banville, 2017), and others (for example, see (Bodine et al., 2001a,b; Driscoll and Goldberg, 1989; Houde et al., 2010; Lecker et al., 2004; Sandri et al., 2004; Temparis et al., 1994)). In the sections that follow, we use the terms proteasome and 26S proteasome interchangeably.

4. Interrelationship between the proteasome and mTORC1

Based on what is known about the functions of the two complexes (mTORC1 and 26S proteasome) in modulating cellular protein content, namely, that mTORC1 is anabolic while 26S is catabolic, the simplest prediction would be that they would function in a counter- regulatory manner. Thus, if there is an increase in the activity of the proteasome, the activity of mTORC1 would be suppressed, and vice versa. Consistent with this, in skeletal muscle and myocytes, conditions of abundance of amino acids, insulin/IGF-1 treatment, and resistance training are usually associated with elevated abundance/activities of mTORC1 and

reduced abundance/activities of the proteasome. Catabolic environments, including amino acid starvation, infection with pathogenic bacteria, treatments with inflammatory cytokines, and muscle disuse, are usually associated with elevated proteolysis and increased abundance/activities of the proteasome, along with suppressed activity of mTORC1 (for example see (Glass, 2005; Stewart et al., 2008; Stitt et al., 2004)). However, data to date indicates that this is an oversimplification of the relationship. Below we describe specific effects of the proteasome on mTORC1, and vice versa which indicate a more sophisticated relationship between these two complexes.

4.1. Impact of the proteasome on mTORC1 assembly/functions

As stated in section 4.0, the simplest model would be that an increase in proteasome activity should occur in tandem with decreased mTORC1 assembly and activity. In skeletal muscle wasting conditions such as starvation, cancer cachexia, chronic kidney diseases, and denervation, there is usually an increase in proteasomal content and/or activities (Bodine et al., 2001a,b; Hobler et al., 2017; Lecker et al., 2004; Tawa Jr., Odessey, and Goldberg, 1997). Such conditions are also typically associated with reduced mTORC1 activity (Bodine et al., 2001a,b; Milan et al., 2015). However, whether the increase in proteasomal activity is causally linked to suppressed mTORC1 function has not been tested.

Studies on the effect of targeted upregulation of proteasomal content and/or activity on mTORC1 functions are quite limited. The simplest model would be that proteasomal degradation of an mTORC1 subunit or integral proteins would lead to an upregulation or down regulation of mTORC1 functions, depending on whether the mTORC1 subunit or interacting protein so degraded is a suppressor or activator of mTORC1 function, respectively (see steps 3, 7–8 in Fig. 4). Evidence in support of this type of interaction is the proteasomal degradation of the mTORC1 subunit and inhibitor, DEPTOR ((Gao et al., 2011; Peterson et al., 2009; Y. Zhao et al., 2011). Here, the cullin-RING ubiquitin ligase $SCF^{\beta TrCP}$-dependent ubiquitination of DEPTOR targets it for degradation by 26S proteasome, with subsequent activation of mTORC1 (and mTORC2). Conversely, another SCF-type E3 ligase, SCF^{FBXW7}, mediates proteasomal degradation of mTOR (Mao et al., 2008). Also, there is evidence that RAPTOR too is degraded by the proteasome (Bridges et al., 2017; Choi et al., 2014). Either or both scenarios would decrease mTORC1 assembly and activity. Just as prolonged autophagy (> 4 h) would lead to accumulation of amino acids that can then increase mTORC1 activity (Yu et al., 2010), step 4 in Fig. 4 shows that increased degradation of cellular proteins by the proteasome (for example, in response to starvation) would be predicted to lead to increased intracellular free amino acid concentrations (step 5) (Suraweera et al., 2012; Vabulas and Hartl, 2005; Y. Zhang et al., 2014), which can then increase mTORC1 activity (step 8). This has been demonstrated in mouse tibialis anterior and gastrocnemius skeletal muscles, whereby mTORC1 induction and increased ribosome biogenesis hours after denervation is suppressed when the proteasome is inhibited (Quy et al., 2013), likely due to a reduction of proteasome-derived free amino acids. Finally, partial proteolysis of some protein substrates by the proteasome can lead to functional activation of such proteins (Bugno et al., 2015; Z. Zhang et al., 2015). Although yet to be demonstrated, there is no reason to suppose that the 26S proteasome cannot regulate the processing of an mTORC1 subunit/s in a similar manner and as such activate or suppress the complex, depending on whether the protein so processed is an activator or inhibitor of mTORC1 (see steps 6 and 8 in Fig. 4).

It is also worth noting that the abundance of many upstream regulators of mTORC1 is regulated by the proteasome. For example, following ubiquitination by the cullin-RING ubiquitin ligase $SCF^{\beta TrCP}$, REDD1, a negative upstream regulator of mTORC1, is degraded by the proteasome (Katiyar et al., 2009). Positive upstream regulators of mTORC1, including insulin receptor substrates (IRS, (Nakao et al., 2009; J. Shi et al., 2011; R. Song et al., 2013; Yi et al., 2013) and AKT (Balaji et al., 2018; Suizu et al., 2009) can also be degraded by the proteasome. This will likely have negative effects on mTORC1 levels and/or functions. However, because modulations of such upstream mTORC1 regulators would likely affect pathways that can indirectly affect mTORC1, these are not reviewed further here.

4.2. Effects of mTORC1 on proteasome levels and/or functions

Given the antagonistic nature of their functions, an increase in mTORC1 activity should occur in parallel with a decrease in proteasomal content and/or activity. Inhibition of mTORC1 leads to decreased protein synthesis and reduced tissue protein mass (Abraham, 2002; Ben-Sahra and Manning, 2017; Saxton and Sabatini, 2017). This is also observed in skeletal muscle cells and tissues (Adegoke et al., 2012; Bodine et al., 2001a,b; Risson et al., 2009). Since mTORC1 inhibition would also promote autophagy and, as discussed below, may promote accumulation of proteasome subunits, this inhibition might also lead to an increase in proteolysis, again leading to reduced tissue protein mass. However, whether mTORC1 inhibition would promote accumulation or degradation of proteasomal subunits is currently contested (see below).

The effect of mTORC1 on the proteasome can be predicted to occur at multiple levels. Because the subunits of the proteasome are all proteins, mTORC1 can affect their abundance and therefore complex assembly and function by increasing the rates of synthesis of these subunits (step 16 in Fig. 4), as has been demonstrated for mTORC1-induced increase in abundance of proteasomal subunits via NRF 1 (nuclear respiratory factor 1) (Bugno et al., 2015). Activation or suppression of the proteasome would also result from, respectively, an mTORC1-induced synthesis of a proteasome activator (step 16), or inhibitor (Step 13). Finally, phosphorylation is a post-translational modification (PTM) that can regulate proteasome function (step 14 and 17 in Fig. 4). Phosphorylation of proteasomal subunits by a number of serine threonine kinases, including dual-specific tyrosine-regulated kinase 2 (Guo et al., 2016), protein kinase A (Marambaud et al., 1996; Zong et al., 2006) and others (reviewed in (Guo et al., 2017)) can activate and promote proteasome activity. Other kinases, including C-Abl and Arg (ABL-related gene product) and p38 catalyze inhibitory phosphorylation of the proteasome (reviewed in (Guo et al., 2017)). So far, mTORC1 itself has not been implicated in the phosphorylation of proteasomal subunits. However, it has also not been excluded.

The specific consequences of experimental mTORC1 inhibition/activation on proteasome abundance and function are currently debated. On one side, there is evidence that accumulation of proteasomal subunits and or induction of proteasomal activity ensue when mTORC1 is inhibited (Rousseau and Bertolotti, 2016; Jinghui Zhao et al., 2015). Consistent with this, an increase in PSMB5, a β-subunit of the 20S particle, was found in muscle of the common marmoset after chronic treatment with rapamycin (Lelegren et al., 2016). However, others have reported that mTORC1 activation increases accumulation of proteasomal subunits and activity (Y. Zhang et al., 2014). Furthermore, in conditions under which mTORC1 would be suppressed (amino acid starvation), proteasomal subunits are degraded in a ubiquitination-dependent, autophagy-mediated process (Cohen-Kaplan et al., 2016). In a much earlier study in B and T lymphocytes, mTORC1 inhibition by rapamycin suppressed the expression (mRNA and protein) of the alpha and beta subunits of PA28, a proteasome activator. Rapamycin also suppressed proteasome activity ((X. Wang et al., 1997). As discussed by Chantranupong and Sabatini (Chantranupong and Sabatini, 2016), the apparent differences in the results of these studies may reflect disparities in the duration of mTORC1 inhibition. In nutrient/growth factor deficient environments, short term mTORC1 inhibition will increase proteolysis via elevated proteasome activity (steps 4–5 in Fig. 4) and autophagy. Amino acids so generated would ultimately lead to reactivation of mTORC1 which would favor cell survival (step 8). With unrestricted prolonged mTORC1 activation, however, increased

proteasome activity might serve to prevent nutrient depletion (steps 18–19 in Fig. 4), although it is not clear what cellular signal would lead to elevated proteasomal activity under such conditions. We have shown that REDD1 is required to maintain mTORC1 in a suppressed state during prolonged serum deprivation, thereby reducing cell death (Dennis et al., 2013). This is likely mediated by preventing cellular nutrient exhaustion. Whether this effect of REDD1 is causally linked to the activation of UPS remains to be examined.

As depicted in steps 11 and 12 of Fig. 4, it is also conceivable that conditions in which mTORC1 activation is incessant might lead to endoplasmic reticulum stress, as a result of an imbalance in mRNA translation and chaperone availability/function (Ozcan et al., 2008). Indeed, deletion of TSC2 in cells and mice, which renders mTORC1 constitutively active, leads to upregulation of ER stress and unfolded protein response, as measured by increased phosphorylation of PKR-like endoplasmic reticulum kinase (PERK), increased level of spliced form of X-box binding protein 1 (XBP-1 s) and of mRNA of glucose-regulated protein 78 (GRP-78) and C/EBP homologous protein (CHOP) (Ozcan et al., 2008). Such a stress might also arise as a result of the increased rate of synthesis of specific proteins not being matched by corresponding increase in interacting partners with which the proteins normally form functional complexes (Tye et al., 2019). Under either condition, and because increased UPS is a critical component of the ER-associated degradation (ERAD) to prevent proteotoxicity (Mehrtash and Hochstrasser, 2018; Olzmann et al., 2013), increased proteasomal activity could help to restore homeostasis (step 12 in Fig. 4) (Y. Zhang et al., 2014). Along this line, it is interesting to note that diseases linked to abnormal protein aggregation are associated with both unbridled mTORC1 activation and impairments in the UPS (Maiese et al., 2013; Pilla et al., 2017; Shafei et al., 2017).

Mechanistically, data from the studies reviewed above were obtained with the use of rapamycin, TSC1/2 ablation, or manipulation of feeding/growth hormone status. Compared with wild type animals, mice with muscle-specific raptor deletion have smaller skeletal muscle mass and reduced size of individual muscle fibers. They also have decreased mRNA expression of muscle E3 ubiquitin ligases, atrogin-1/muscle atrophy F box (MAFbx) and muscle ring finger 1 (MuRF-1) (Bentzinger et al., 2008). It would be interesting to see how proteasome abundance and activity are regulated in the muscle of those mice.

Finally, many potential substrates of the proteasome, especially those whose ubiquitination is catalyzed by cullin-RING E3 complexes, require prior phosphorylation before they can be ubiquitinated. Some of these phosphorylation reactions are catalyzed by mTORC1 or mTORC1-S6K1, as discussed previously for DEPTOR and is the case for PDCD4 (Dorrello et al., 2006). Other examples include mTORC1-induced serine 422 phosphorylation of IRS1 (Yoneyama et al., 2018) and serine 395 phosphorylation of WIPI 2 (W. Wan et al., 2018), a critical component of autophagosome formation, prior to ubiquitination and proteasomal degradation of these proteins. Therefore, mTORC1 can directly funnel substrates to the proteasome via its phosphorylation of substrates prior to ubiquitination and subsequent degradation by the proteasome.

5. Reflection

Many cell cycle regulators/tumor suppressor proteins are substrates of the proteasome (Adams, 2004; Finley, 2009) and the abundance of many of them, including p53 and p27, is low in cancer and negatively correlates with tumor progression (Borriello et al., 2011; Jovanović et al., 2019; Yuniati et al., 2019). As a result, proteasome inhibitors like bortezomib/velcade, ixazomib, and carfilzomibare are either in clinical trial or are approved for treatment of selected cancers, mostly hematological cancers (Manasanch and Orlowski, 2017). Likewise, because mTORC1 is a regulator of cell size and number, mTOR (as mTORC1 or mTORC2) inhibitors (including temsirolimus, everolimus, and deforolimus (all targeting mTORC1), AZD8055 (targeting both)) are in clinical trials or are approved as treatments for some cancers, including glioblastomas, renal cell carcinomas and neuroendocrine tumors of pancreatic origin (reviewed in (Jhanwar-Uniyal et al., 2019; O'Donnell et al., 2018; Saxton and Sabatini, 2017). Therefore, inhibiting either of these super complexes appears to hold treatment potential against some cancers. Although there is evidence for beneficial effects of mTORC1 inhibition during aging (reviewed in (Gilley et al., 2013; Johnson et al., 2013; Sharples et al., 2015; Weichhart, 2018), studies with rapamycin and related drugs, or genetic mTORC1 inhibition showed deleterious effects on muscle mass and functions (for selected references, see (Cunningham et al., 2007; Dickinson et al., 2011; Marabita et al., 2016; M. Wan et al., 2006; Q. Zhang et al., 2019)(Bentzinger et al., 2008; Risson et al., 2009)). On the other hand, proteasomal inhibition attenuates proteolysis and loss of muscle mass (A. Z. Caron et al., 2011; FANG et al., 1998; Tawa Jr. et al., 1997) and functions (Agten et al., 2012; van Hees et al., 2011) seen in muscle atrophy conditions, although there is evidence that proteasomal inhibitors not only inhibit muscle proteolysis but also synthesis (Kadlčíková et al., 2004; Muthny et al., 2009). The severity of effect of the inhibition might also depend on the degree to which the proteasome function is impaired. For example, genetic deletion of Rpt3, a critical proteasomal subunit, is associated with poor muscle growth and function (Kitajima et al., 2014). The effects of combinatory proteasomal and mTORC1 inhibition on skeletal muscle has not been systematically examined. Phase I/II clinical trials of a combined therapy of everolimus (mTORC1 inhibitor) and Bortezomib (proteasome inhibitor) in some cancers, including non-Hodgkin lymphoma (Hill et al., 2018) and in Waldenstrom macroglobulinemia (a type of lymphoma) (Ghobrial et al., 2015) patients have been reported. It would be interesting to see what the effects of combinatorial mTORC1-proteasomal inhibition on muscle and whole body protein homeostasis would be. However, cancer treatment with proteasome inhibitors is associated with some side effects, including neuropathy (in some studies, incidence is up to 80% among patients receiving the treatment), thrombocytopenia (abnormally low level of platelets), neutropenia and diverse cardiovascular abnormalities (reviewed in (Manasanch and Orlowski, 2017)). Likewise, use of mTORC1 inhibitors in cancer treatment, alone or in combination with other kinase inhibitors, is associated with many side effects, including hyperglycemia, lymphopenia, thrombocytopenia, pneumonitis and hepatotoxicity (reviewed in (O'Donnell et al., 2018)). The use of either class of drugs is also associated with common side effects such as nausea, diarrhea and vomiting. Treatment regimens that combine inhibitors of both mTORC1 and the 26 S proteasome will likely be associated with even more severe adverse effects. These adverse effects will need to be catalogued and addressed before such combinatorial drug regimens can be considered as options in limiting muscle wasting in cachectic cancer patients.

Acknowledgments

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