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mTORC1 senses stresses: Coupling stress to proteostasis

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Abstract

Beyond protein synthesis and autophagy, emerging evidence has implicated mTORC1 in regulating protein folding and proteasomal degradation as well, highlighting its prominent role in cellular proteome homeostasis or proteostasis. In addition to growth signals, mTORC1 senses and responds to a wide array of stresses, including energetic/metabolic stress, genotoxic stress, oxidative stress, osmotic stress, ER stress, proteotoxic stress, and psychological stress. Whereas growth signals unanimously stimulate mTORC1, stresses exert complex impacts on mTORC1, most of which are repressive. mTORC1 suppression, as a generic adaptive strategy, empowers cell survival under various stressful conditions. In this essay, we provide an overview of the emerging role of mTORC1 in proteostasis, the distinct molecular mechanisms through which mTORC1 reacts to diverse stresses, and the schemes exploited by cancer cells to circumvent stress-induced mTORC1 suppression. Hence, acting as a stress sensor, mTORC1 intimately couples stresses to cellular proteostasis.

Keywords

mTORC1; proteostasis; stress sensor; SAPK/JNK; HSF1

Introduction

As one of the fundamental building blocks of cells, proteins are vital to life. Unsurprisingly, the cellular proteome is subjected to tight and dynamic regulation at the points of protein synthesis, folding and degradation. As a consequence, the cellular proteome exists in dynamic equilibrium: a delicate state referred to as proteome homeostasis or proteostasis [1]. Congruent with its paramount importance, a wealth of evidence has implicated proteostasis in a broad range of pathophysiological conditions in humans [1].

mTORC1 governs proteostasis

One key component of this homeostatic network is protein synthesis. Among the various pathways governing protein production inside cells is mechanistic target of rapamycin (mTOR) signaling. First discovered in 1991 in yeasts [2], mTOR is a Ser/Thr kinase that belongs to the phosphoinositide kinase-related family of protein kinases (PIKKs) [3]. After

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CONFLICTS OF INTEREST

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two decades of intense studies, a great deal of knowledge has been gleaned about mTOR. Inside cells, mTOR is assembled into two distinct multi-component protein complexes: mTOR complex 1 (mTORC1) and complex 2 (mTORC2) [3]. mTORC1 comprises mTOR, regulatory associated protein of mTOR (RAPTOR), mammalian lethal with SEC13 protein 8 (mLST8 or GβL), proline-rich AK transforming (AKT) substrate 40kDa (PRAS40), DEP domain containing mTOR-interacting protein (DEPTOR), and newly identified telomere maintenance 2 (TEL2) and TEL2 interacting protein 1 (TTI1) [3,4]. While mTOR is the core kinase, RAPTOR is proposed to function as a scaffold protein that recruits the substrates for phosphorylation by mTOR [5]. The RAPTOR-mTOR interaction can be either loosened or tightened depending on the stimuli. For instance, whereas rapamycin disrupts this interaction, amino acid deprivation strengthens it [6]. Therefore, the precise impacts of RAPTOR on mTOR may be complex: at the very least, they remain to be fully elucidated. mLST8/GβL, by interacting with mTOR's kinase domain and stabilizing the RAPTOR-mTOR interaction, positively regulates mTORC1 [7]. However, this model is challenged by the observation that RAPTOR-mTOR interactions are not impaired in mice deficient in *mLST8/GβL* [8]. In contrast to RAPTOR, the AKT substrate PRAS40 is generally believed to be a negative regulator of mTORC1 [9]. Through direct interactions with RAPTOR, PRAS40 blocks the binding of substrates to mTOR [10, 11]. The phosphorylation of PRAS40 at Thr246 by AKT causes its dissociation from RAPTOR [10], thereby relieving the suppression. Like PRAS40, DEPTOR also negatively impacts mTORC1 by binding to the FRAP-ATM-TTRAP (FAT) domain of mTOR directly [12].

mTORC2, like mTORC1, also contains mTOR, mLST8/GβL, DEPTOR, TEL2 and TTI1. In addition to these common subunits, mTORC2 consists of three unique components additionally—namely rapamycin-insensitive companion of mTOR (RICTOR), mammalian stress-activated MAP kinase-interacting protein 1 (mSIN1), and protein observed with RICTOR (PROTOR) [3]. While RICTOR is necessary for the assembly of mTORC2 [13], mSIN1 plays a critical role in maintaining the RICTOR-mTOR interaction [14]. Congruently, both RICTOR and mSIN1 positively impact mTORC2 activity. By contrast, PROTOR is dispensable for mTORC2 assembly and appears only to affect the phosphorylation of selective substrates of mTORC2 in a tissue-specific manner [15]. Sharply contrasting with its dispensability for the RAPTOR-mTOR interaction, *in vivo* studies confirm the necessity of mLST8/GβL for the RICTOR-mTOR interaction [8]. Similar to its impact on mTORC1, DEPTOR negatively regulates mTORC2 as well [12].

mTORC1 and mTORC2, despite sharing the very same core catalytic subunit, differ greatly in substrate recognition. The prominent substrates for mTORC1 include eukaryotic translation initiation factor 4E–binding protein 1 (eIF4E–BP1) [16], ribosomal protein S6 kinase 1 (S6K1) [16], unc-51 like autophagy activating kinase 1 (ULK1) [17], autophagy related 13 (ATG13) [18,19], phosphatidic acid phosphatase LIPIN1 (LPIN1 or PAP1) [20], growth factor receptor bound protein 10 (GRB10) [21], and cytoplasmic linker protein 170 (CLIP-170) [22]. Accordingly, mTORC1 controls protein translation, autophagy and lipogenesis [3]. By contrast, mTORC2 phosphorylates AKT [23], protein kinase C (PKC) [13], and serum/glucocorticoid regulated kinase 1 (SGK1) [24,25], thereby controlling, cell survival, cytoskeleton organization, and stress responses [3].

A plethora of evidence has unequivocally pinpointed a crucial role of mTORC1 in governing protein translation via two key substrates--eIF4E–BP1 and S6K1 [3,16]. The mTORC1-mediated Thr389 phosphorylation leads to dissociation of S6K1 from the eukaryotic initiation factor complex 3 (eIF3) [26], followed by the phosphoinositide-dependent kinase 1 (PDK1)-mediated S6K1 Thr229 phosphorylation [27]. Upon activation, S6K1 phosphorylates ribosomal protein S6 (RPS6) to stimulate ribosomal biogenesis [28], eukaryotic elongation factor 2 kinase (eEF2K) to de-repress translational elongation [29], as well as eIF4B to heighten translational initiation [26,30]. Following S6K1 dissociation, mTORC1 accesses eIF4E–BP1, which interacts with eIF4E at the 5' cap structures of mRNAs [31]. The mTORC1-mediated Thr37/46 and Ser65/Thr70 phosphorylation releases eIF4E–BP1 from eIF4E, thereby enabling the assembly of eIF4F complex that will recruit the 40S ribosomal subunits to the cap structures to initiate translation [31]. In aggregate, mTORC1 is a key player in controlling protein synthesis.

Beyond protein production, mTORC1 also regulates other aspects of proteostasis. As an intracellular lysosome-based self-degradation mechanism, autophagy impacts proteostasis through clearance of aggregated proteins [32]. By phosphorylating ULK1 and ATG13[17–19], two key components of the autophagy initiation complex, mTORC1 suppresses autophagy. Mechanistically, the mTORC1-mediated Ser757 phosphorylation impedes the activating phosphorylation of ULK1 at Ser317 and Ser777 by the metabolic sensor AMP-activated protein kinase (AMPK) [17]. Recently, mTORC1 has further been implicated in regulating proteasomal degradation, another key protein-quality control mechanism. It was reported that mTORC1 activation stimulates proteasome biogenesis via the nuclear factor erythroid-derived 2-related factor 1 (NRF1)-mediated transcription of proteasome subunit genes [33], suggesting coordinated protein synthesis and degradation. However, this was challenged by the observation that mTORC1 inhibition promotes proteasomal degradation via enhanced protein ubiquitination [34]. Apparently, more thorough studies are warranted to delineate how mTORC1 affects the ubiquitin-proteasome system (UPS). In addition to protein degradation, mTORC1 also influences cellular chaperoning capacity under proteotoxic stress. It has been widely recognized that cells cope well with proteotoxic stress by mobilizing a potent transcriptional program named the heat-shock, or proteotoxic, stress response (HSR/PSR) [35]. The most notable feature of this stress response is rapid induction of heat-shock proteins (HSPs) or molecular chaperones [35]. Under proteotoxic stress, HSPs are essential to cellular proteostasis by safeguarding proper protein folding, resolving protein misfolding, and promoting the ubiquitination and degradation of damaged proteins that are beyond repair [35]. Of note, under proteotoxic stress mTORC1 is required for robust translation of both heat shock factor 1 (*HSF1*) and highly transcribed *HSP* mRNAs [36]. Thus, mTORC1 contributes to cellular proteostasis through translational augmentation of the HSR/PSR [36]. Collectively, these findings highlight an important role of mTORC1 in protein-quality control, beyond its well-known impact on protein-quantity control (Fig. 1).

Diverse extracellular and intracellular cues regulate mTORC1

In light of its biological importance, unsurprisingly, mTORC1 is under stringent and complex regulations. The Ras-homolog expressed in brain (RheB), a small GTPase that physically interacts with and activates mTORC1 [37], is an additional immediate regulator

of mTORC1. Furthermore, RheB is directly inhibited by the tuberous sclerosis complex 1 and 2 (TSC1/2) [38,39], well-known tumor suppressor complexes. Recently, a third core subunit of this complex, TBC1 domain family member 7 (TBC1D7), has been identified [40]. TSC1-TSC2-TBC1D7 complexes act as GTPase-activating proteins (GAP) that inhibit RheB activity by converting RheB-GTP into RheB-GDP [38,39]. In this way, mTORC1 is critically regulated by the TSC-RheB cascade.

mTORC1 senses growth factors and nutrients

Two major signals that stimulate mTORC1 are growth factors, including insulin and insulin-like growth factor 1 (insulin/IGF-1), and amino acids [3]. In response to growth stimulation, the phosphoinositide 3-kinase (PI3K)/AKT and rat sarcoma small GTPase/rapidly accelerated fibrosarcoma oncogene /MAP-ERK kinase/extracellular signal-regulated kinase/90KDa ribosomal protein S6 kinase (RAS/RAF/MEK/ERK/RSK) signaling pathways become activated. Subsequently, AKT phosphorylates TSC2 at Ser939 and Thr1462, leading to inactivation of the TSC complex [41,42]. The ERK-mediated Ser540/664 and RSK1-mediated Ser1798 phosphorylation of TSC2 achieve the similar effects [43,44].

Despite the well-known fact that amino acids, especially leucine, are an essential activator of mTORC1 [45], the underlying molecular mechanisms remain elusive until recently. Studies have now revealed that on the lysosomal surface a large protein complex, which at least comprises vacuolar H+-ATPase (v-ATPase), RAGULATOR (a pentameric complex consisting of LAMTOR1–5), and Ras-related GTP-binding protein (Rag) small GTPases, mediates the amino acid-sensing of mTORC1 [45]. Within this complex, v-ATPase physically interacts with RAGULATOR, a guanine nucleotide exchange factor (GEF) for RagA/B GTPases [46,47]. In response to amino acid stimulation, v-ATPase activates RAGULATOR [46,47], which may involve amino acid-dependent changes in v-ATPase assembly [48]. Subsequently, the GTP-loaded RagA/B that is heterodimerized with the GDP-loaded RagC/D recruit inactive mTORC1 from the cytosol to the lysosomal surface, where it becomes activated by RheB [49,50]. Sestrin2 was identified recently as an intracellular sensor for leucine. Binding of leucine causes dissociation of Sestrin2 from GAP activity towards Rags 2 (GATOR2), a protein complex positively regulating mTORC1 by inhibiting GATOR1 [51], another protein complex that acts as a GAP for RagA/B [52]. Moreover, two arginine sensors have also been identified. One is solute carrier family 38 member 9 (SLC38A9), a lysosomal transmembrane protein that interacts with both Rag GTPases and RAGULATOR [53]. The other is cellular arginine sensor for mTORC1 (CASTOR1), a protein physically interacting with and inhibiting GATOR2 [54]. Binding of arginine to CASTOR1 causes its dissociation from GATOR2, thus activating GATOR2 and relieving the suppression of RagA/B-GTP by GATOR1 [54].

mTORC1 senses a diversity of stresses

In addition to growth factors and amino acids, mTORC1 also senses and responds to a large variety of stresses. Under this scenario, mTORC1 becomes suppressed, likely reflecting a general cellular strategy to adapt to stressful conditions. Accumulating studies have started unraveling the molecular regulations of mTORC1 by stresses.

mTORC1 is suppressed by energetic/metabolic stress—Cellular energetic stress is hallmarked by the decline of ATP and/or increase of AMP levels inside cells. As a consequence, AMPK, a key cellular metabolic sensor, becomes mobilized [55]. Among the numerous AMPK substrates are TSC2 and RAPTOR. While the AMPK-mediated Ser1387 (Ser1345 in the rat counterpart) phosphorylation activates TSC2 [56], phosphorylation of RAPTOR at Ser722 and Ser792 by AMPK induces the binding of 14-3-3 proteins, leading to RAPTOR inhibition [57]. Furthermore, independently of AMPK, energy depletion suppresses mTORC1 via the p38 mitogen-activated protein kinase (p38 MAPK) signaling. Following 2-deoxy-D-glucose treatment, p38 regulated/activated kinase (PRAK) directly phosphorylates RheB at Ser130, a modification that impairs the GTP/GDP binding of RheB and leads to mTORC1 inactivation [58]. In addition, under energetic stress p38β phosphorylates forkhead box class O (FOXO) transcription factors, which induce BCL2 interacting protein 3 (BNIP3) expression [59]. BNIP3, in turn, interacts with and inactivates RheB, leading to mTORC1 suppression [59]. Moreover, energetic stress can also suppress mTORC1 via TEL2-TTI1-TTI2 (TTT)-RUVBL1/2 [60], an AAA^+ ATPase-containing protein complex that is implicated in regulating PIKKs [61]. Depletion of glucose and glutamine causes disassembly of the mTORC1-interacting TTT-RUVBL1/2 complex, impeding mTORC1 dimerization and lysosomal translocation [60]. Thus, via multiple distinct pathways energetic stress suppresses mTORC1.

mTORC1 is both suppressed and stimulated by oxidative stress—Imbalance between cellular reactive oxygen species (ROS) and antioxidants leads to oxidative stress, which has been implicated in a wide array of human pathophysiological conditions, including aging, diabetes, atherosclerosis, neurodegenerative disorders, and cancer [62].

Elevated ROS can activate ataxia telangiectasia mutated (ATM) [63], a key tumor suppressor sensing DNA damage [64]. In turn, ATM suppresses mTORC1 via the liver kinase B1 (LKB1)-AMPK-TSC2 signaling cascade [63]. In addition, under arsenite-induced oxidative stress sperm associated antigen 5 (SPAG5 or ASTRIN), a protein regulating mitotic spindles, sequesters RAPTOR apart from mTORC1 to stress granules (SGs), thereby suppressing mTORC1 [65]. SGs are cytoplasmic aggregates of messenger ribonucleoproteins (mRNPs) that develop under conditions wherein translation is inhibited, such as diverse stresses [66]. Moreover, nemo-like kinase (NLK) has also been shown to play a role in suppressing mTORC1 under oxidative stress [67]. Through direct phosphorylation of RAPTOR at Ser863, NLK disrupts RAPTOR-Rag GTPase interactions, thereby impeding mTORC1's lysosomal translocation and activation [67].

However, oxidants have also been reported to stimulate mTORC1. For example, the cysteine oxidant phenylarsine oxide activates RheB and thereby mobilizes mTORC1 [68]. Moreover, arsenite activates p38β, which leads to mTORC1 activation via phosphorylating RAPTOR [69]. Thus, the impacts of oxidative stress on mTORC1 seem complex, which may, at least in part, be determined by the intensity and duration of stress.

mTORC1 is suppressed by genotoxic stress—Various DNA damages, caused by oxidation, hydrolysis, alkylation, nucleotide mismatch and radiation, elicit genotoxic stress

inside cells. To repair the damage and maintain genome integrity, cells rely on the DNA damage response (DDR) [70].

ATM and ataxia telangiectasia and Rad3-related (ATR) are two key DNA-damage sensors and regulators of the DDR [71]. Like oxidative stress, genotoxic stress activates ATM, which could subsequently suppress mTORC1 through the LKB1-AMPK-TSC2 cascade [63]. Activated ATM can also mobilize tumor protein p53 (TP53), a well-known tumor suppressor, via Ser15 phosphorylation [72]. Interestingly, Sestrin1/2, two target genes of TP53, can either activate the AMPK–TSC2 cascade or inhibit the guanine nucleotide exchange of Rag GTPases, thereby causing mTORC1 suppression [73,74]. In addition, regulated in development and DNA damage responses 1 (REDD1), another TP53 target gene involved in the TP53-mediated apoptosis in response to DNA damage [75], acts as a TSC2 activator through either blockade of 14-3-3 protein binding to TSC2 or inactivation of AKT by recruiting PP2A, thereby suppressing mTORC1 [76,77]. The tumor suppressor phosphatase and tensin homolog (PTEN), whose expression is also induced by TP53 [78], can also suppress mTORC1 by inhibiting PI3K/AKT signaling [79], a well-established signaling pathway that stimulates mTORC1. Moreover, TP53 activation also stimulates *TSC2* expression [80]. Taken together, all these studies indicate mTORC1 suppression as an important aspect of the cellular response to genotoxic stress.

mTORC1 is suppressed by hyperosmotic stress—Unequal osmolarity between intra- and extracellular environments causes flux of water into or out of cells, eliciting osmotic stress [81]. In particular, hyperosmotic stress is referred to as the condition where extracellular osmolarity is higher than intracellular one. Accordingly, cells shrink and become dehydrated, owing to loss of intracellular water, which triggers a broad range of molecular changes, including DNA and protein damage [81].

It has been reported that under hyperosmotic stress NLK, similarly to under oxidative stress, mediates mTORC1 suppression by phosphorylating RAPTOR at Ser863 to disrupt the RAPTOR-Rag interactions [67]. Moreover, hyperosmotic stress can also inactivate AKT, likely via a Calyculin-A-sensitive phosphatase, to promote TSC2 activation, thereby suppressing mTORC1 [82]. Interestingly, hyperosmotic stress was reported to cause sequestration of both mTORC1 and the dual specificity tyrosine-phosphorylation-regulated kinase 3 (DYRK3) into SGs [83]. During stress DYRK3 sequestration prevents dissolution of SGs and mTORC1 release [83]. However, following stress DYRK3 directly phosphorylates and inactivates PRAS40, an inhibitory component of mTORC1, thereby re-activating mTORC1 [83]. Of interest, emerging studies suggest SGs as an important stress-inducible compartment for mTORC1 suppression during stress. In contrast to hyperosmotic stress, little is known about the impacts of hypo-osmotic stress on mTORC1.

mTORC1 is both suppressed and stimulated by ER stress—The endoplasmic reticulum (ER) is a central organelle where secreted and membrane-bound proteins are sorted and processed. ER homeostasis is vital to the health of cells, especially those specialized in secretion. Perturbation of this homeostasis, due to either external insults or internal defects, inevitably causes accumulation of many misfolded and aggregated proteins inside the ER lumen, a severely adverse condition widely referred to as ER stress [84]. To

counteract this type of stress, cells have evolved a defensive mechanism named the ER stress response or unfolded protein response (UPR) [84].

Protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1 (IRE1) and activating transcription factor 6 (ATF6) are the three principal ER-stress sensors that mediate the UPR [84]. Given the nature of ER stress, attenuation of protein translation is not surprising. Indeed, under ER stress, activated PERK phosphorylates eIF2α, a subunit of eIF2 that is essential for the ternary complex (TC) formation [85], at Ser51 [86]. This phosphorylation blocks TC formation and thereby inhibits the translation initiation. In stark contrast to this wellilluminated mechanism, whether and how ER stress impacts mTORC1 are much less clear. Nonetheless, it has been reported that PERK activation following ER stress leads to selective translation of ATF4, a transcription factor mediating the UPR, via the upstream open reading frame (uORF) mechanism [87]. In turn, ATF4 induces the expression of REDD1 and tribbles pseudokinase 3 (TRIB3) [88,89]. While REDD1 is an activator of TSC2, TRIB3 is a direct AKT inhibitor [90]. Thus, increased REDD1 and TRIB3 both lead to mTORC1 suppression. Importantly, cells deficient in either *Tsc1* or *Tsc2* are hypersensitive to ER stress [91], suggesting the necessity of mTORC1 suppression for surviving ER stress. Congruently, mTORC1 inhibition enhances cellular survival of ER stress, although it was ascribed to blockade of the IRE1-JNK signaling cascade [92]. Conflicting with the reported role of ATF4 in mediating mTORC1 suppression, it was reported that during ER stress ATF4, in cooperation with the C/EBP homologous protein (CHOP), promotes global protein synthesis via transcriptional regulation of target genes involved in protein translation [93]. Similarly, evidence also indicates that ER stress stimulates AKT in the acute phase, thereby leading to mTORC1 activation [92]. Given the translation inhibition already imposed by eIF2α phosphorylation, it remains possible that the initial mTORC1 activation may exert effects other than protein translation.

Despite these seemingly contradictory findings, it is generally agreed upon that attenuation of protein synthesis promotes survival of ER stress, at least during the acute phase; and, during the chronic phase protein synthesis resumes. In contrast to the evident role of eIF2α in attenuating protein translation under ER stress, the implication of mTORC1 remains obscure.

mTORC1 is suppressed by proteotoxic stress—While there are considerable amounts of secreted and transmembrane proteins inside cells, however, a large proportion of the entire cellular proteome are consisted of proteins that are not processed in the ER. Instead, they mature and reside in the cytosol and/or nuclei. Molecular chaperones or HSPs, the counterparts of ER chaperones such as BiP/GRP78, are responsible for the proper folding, transportation, assembly, as well as degradation of these cytosolic and nuclear proteins, thereby playing a pivotal role in preserving cellular proteostasis [1,94]. Disruption of this equilibrium will provoke proteotoxic stress and, in turn, mobilize the powerful HSR/PSR [35]. Similar to the UPR, the HSR/PSR is also a transcriptional program that is primarily governed by HSF1 [95,96].

It has been long recognized that classic proteotoxic stressors, such as heat shock, causes global inhibition of protein synthesis. Again, this has been mainly ascribed to eIF2α

phosphorylation [97]. In light of the importance of mTORC1 in controlling translation, surprisingly, little is known about whether and how mTORC1 responds to proteotoxic stress. It was reported that HSPs, in particular HSP90, help to assemble mTORC1 [98]. Owing to the titration by elevated levels of misfolded proteins under heat stress, the mTORC1-chaperoning activity of HSP90 is diminished, leading to disassembly and suppression of mTORC1 [98]. Given the abundance of cellular HSP90, this mechanism likely takes effect under chronic or intense proteotoxic stress where HSP90's availability becomes a limiting factor. By contrast, it remains unclear how mTORC1 reacts to proteotoxic stress acutely.

Prompt attenuation of general protein translation would be a logical reaction of cells to adapt to and survive proteotoxic stress. In line with this notion, a recent study revealed that diverse proteotoxic stressors, including heat shock and proteasome inhibitors, potently suppress mTORC1 and its mediated protein translation [36]. Of note, this is an acute response. For example, following proteasomal inhibition, mTORC1 activity begins to decline within 10 minutes, accompanied by concurrent Stress-activated protein kinase/c-Jun NH(2)-terminal kinase (SAPK/JNK) activation [36]. Mechanistically, proteotoxic stressors with distinct modes of action universally trigger JNK activation, which is both necessary and sufficient for mTORC1 suppression [36]. Of particular interest, JNK physically interacts with and phosphorylates mTORC1 [36], intimately integrating proteotoxic stress with protein translational control. Strikingly, JNK associates with mTORC1 in a constitutive manner and proteotoxic stress does not enhance this physical interaction, rather triggers JNK activation [36]. Following activation, JNK phosphorylates both RAPTOR at Ser863 and mTOR at Ser567, respectively, leading to mTORC1 disassembly [36]. This disassembly is partial, selectively excluding mTOR and its positive regulator mLST8/GβL from the complex but retaining JNK-RAPTOR-PRAS40 interactions [36]. Collectively, these new findings support the concept that mTORC1 is poised to respond to proteotoxic stress promptly with JNK as an integral sensor (Fig. 2).

Suppression of general protein translation, albeit beneficial to proteotoxic-stress adaptation by lessening overall proteomic burden, also creates a dilemma. Marked elevation of HSP expression is vital to surviving proteotoxic stress and, ultimately, restoring cellular proteostasis. Uncontrolled translation inhibition would diminish HSP production, dampening the HSR/PSR and exacerbating cell death. Thus, cells need to develop a means to prevent profound translational inhibition during proteotoxic stress. Indeed, JNK activation by proteotoxic stress is tightly modulated by HSF1, the master regulator of the HSR/PSR. Through physical interactions, HSF1 sequesters JNK away from mTORC1 [36], thereby ensuring attenuation, but not deep repression, of protein translation. Of great interest, HSF1 exerts this effect independently of its canonical transcriptional action [36]. This mode of action highlights that the abundance of HSF1 proteins governs the severity of mTORC1 suppression by proteotoxic stress. Beyond the stress response, importantly, this regulation has profound impacts on normal cellular and organismal growth. Cells and mice deficient for *Hsf1* display elevated JNK activation, resulting in suppressed mTORC1 signaling and protein translation, and, ultimately, diminished cell and body size [36].

In aggregate, acting like a rheostat, HSF1 elegantly attunes mTORC1's response to proteotoxic stress. Importantly, HSF1, through regulations of both mTORC1 and the HSR/

PSR, intimately coordinates the protein quantity- and quality-control machineries. Thereby, a healthy cellular proteostasis is safeguarded.

mTORC1 is suppressed by psychological stress—It has been well established that protein translation is key to synaptic plasticity, learning and memory [99]. Compared to the various physical stresses discussed above, the knowledge of whether and how psychological stress impacts mTORC1 is scarce. Nonetheless, emerging studies start shedding light on this issue.

In rats, chronic unpredictable stress (CUS) causes mTORC1 suppression through induction of REDD1, a negative mTORC1 regulator that activates TSC2, in the prefrontal cortex region (PFC) [100]. Importantly, *Redd1* deficiency markedly reverses the mTORC1 suppression, synaptic loss, and depressive behavior induced by CUS in rats [100]. Supporting a causative role of mTORC1 suppression in depressive disorders, ketamine, a N-methyl-D-aspartic acid receptor (NMDAR) antagonist that is currently on clinical trials for treating major depressive disorder (MDD), activates mTORC1 in the PFC of rats, which underlies its rapid antidepressant effects [101].

Interestingly, acute immobilization stress can induce JNK activation in the hippocampus, causing deficits in associative learning [102]. Moreover, JNK is also activated by NMDAR [103], and NMDAR activation leads to mTORC1 suppression [104]. Although this suppression has been ascribed to impaired neuronal arginine uptake, owing to depletion of cell surface cationic amino acid transporters 1/3 (CAT1/3) [104], it remains elusive whether JNK activation also contributes to mTORC1 suppression in this context (Fig. 2). In further support of a causative role of JNK activation in anxiety and depression, in mice *Jnk1* deletion promotes hippocampal neurogenesis, alleviating anxiety and depressive-like behaviors [105]. Taken together, further efforts are warranted to fully elucidate the roles of mTORC1 and JNK in psychological stress, which is crucial to our better understanding of anxiety and depression, and may further open new therapeutic avenues.

mTORC1 suppression: a common theme of stress adaptation

Under ER or proteotoxic stress, cells mitigate protein synthesis to reduce proteomic input, a key strategy enabling more efficient proteomic repair and proteostasis restoration. Then, why does mTORC1 suppression also occur under numerous other types of stress?

Interplay between different cellular stresses may be one simplified explanation. For instance, hyperosmotic stress can induce protein misfolding as well, which likely signals mTORC1 suppression. Alternatively, osmotic stress may affect mTORC1 assembly directly. Oxidative stress can also lead to protein oxidation, a type of protein damage that likely elicits proteotoxic stress and subsequent mTORC1 suppression.

Another simplified explanation is energy conservation. To adapt to energetic stress, it is imperative for cells to minimize anabolic processes, among which protein synthesis consumes a large amount of cellular ATP. Attenuation of protein synthesis would markedly diminish ATP consumption, empowering cells to restore energy homeostasis. Why does genotoxic stress also suppress mTORC1? One of the plausible explanations is oxidative

stress, as genotoxic stressors, including DNA alkylating agent, UV and ionizing radiation, frequently induce intracellular ROS [106–108]. High levels of ROS will cause oxidative stress, which leads to mTORC1 suppression. Another possibility is general transcriptional arrest. It has been known that DNA damage causes transcriptional arrest, through either hyperphosphorylation of RNA polymerase II, which prevents its association with the pre-initiation complex [109] or sequestration of TATA-binding protein (TBP) to damaged DNA, which limits its participation in transcription [110]. With reduced mRNA templates, it would be uneconomical to sustain high-rate protein translation.

Cancer cells elude stress-induced mTORC1 suppression

Unambiguous evidence has demonstrated the critical role of mTORC1 in promoting tumorigenesis. However, cancer cells also experience various stresses constantly from within and without. Inevitably, this constitutively stressed state would restrain robust mTORC1 activation. To eliminate or mitigate this constraint, cancer cells adopt diverse strategies. One of them is dampening the negative regulations of mTORC1. Inactivating mutations in tumor suppressor genes, including *PTEN* [111], the negative regulator of PI3K/AKT signaling, *LKB1* [112], an upstream activator of AMPK, and *TSC1/2* [113], render mTORC1 constitutively active and alleviate stress-induced suppression. Similarly, inactivation of the JNK signaling cascade also occurs in human cancers. Mutations in *MAP2K4/MKK4* and *MAP2K7/MKK7* [114,115], two key upstream kinases of JNK, impair JNK activation, in line with their tumor-suppressive functions [116,117]. Moreover, mutations in *MAPK8/JNK1* and *MAPK9/JNK2* are also identified [114], although the functional consequences remain to be elucidated. Alternatively, cancer cells can alleviate the JNK-mediated mTORC1 suppression through physical sequestration of JNK, as elevated HSF1 expression is widespread in human cancers [94]. Contrary to HSF1 overexpression, in most human cancers the expression of *DEPTOR*, a negative regulatory component of mTORC1, is markedly reduced [12].

In contrast to the de-repressing strategy, activating mutations of positive upstream regulators of mTORC1, including *PI3KCA, AKT, RAS, RAF, MEK*, and RheB [118–121], result in constitutive mTORC1 activation. Furthermore, mutations in *mLST8/GβL* have also been identified in human cancers (COSMIC/http://cancer.sanger.ac.uk), although their functional consequences remain unaddressed. Moreover, cancer cells could select for activating mutations within *mTOR* kinase itself. A number of mTOR-activating mutations have been uncovered in human cancers, some of which result in diminished DEPTOR binding and partial resistance of mTORC1 to nutrient deprivation, and resistance to the REDD1-mediated suppression [122,123]. Therefore, at least some of these activating mutations are expected to render mTORC1 resilient to suppression by other stresses as well.

Conclusions and Perspectives

mTORC1: a generic stress sensor?

It is evident that mTORC1 responds to diverse stresses via distinct mechanisms, some of which are indirect and require nascent transcription and/or translation. Likely, these mechanisms operate in the late-phase or chronic mTORC1 response to stress.

JNK is known to be activated by numerous stresses, including oxidative, osmotic, energetic, genotoxic, and ER stress [124–128]. Given its constitutive association with mTORC1 [36], it is tempting to speculate that mTORC1 senses a wide variety of stress signals immediately via JNK. This configuration is expected to empower mTORC1 to react to stress in a generic and prompt fashion. With the initial work focusing on proteotoxic stress only, further studies are required to confirm this notion in the context of other stresses.

Cellular stress: a double-edged sword in tumorigenesis?

Upon acute stress, reduction in global protein, lipid, and RNA synthesis and arrest of cell cycle progression represent a collective adaptive response enhancing survival and promoting damage repair. These systemic changes are incompatible with the anabolic lifestyle required to sustain malignancy. Thus, acute cellular stress likely antagonizes malignant growth.

Paradoxically, chronic cellular stress may promote malignancy, partly due to the selection pressure that drives the emergence of genetic and/or epigenetic alterations helping them both survive and resist stresses. This is supported by the occurrence of mutations rendering cancer cells refractory to stress-induced mTORC1 suppression [122,123]. In this way, chronic cellular stress may hasten tumor progression and cause the emergence of aggressive malignant phenotypes, analogous to the accelerated evolution by stressful environments [129,130]. This notion, albeit speculative, may have key implications. Chemo- and radiotherapies largely provoke genotoxic stress in cancer cells. Theoretically, these therapies should be administered to elicit acute and drastic cellular stresses. By doing so, cancer cells will be less likely to adapt, survive, and evolve.

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Abbreviations

ER	endoplasmic reticulum
HSF1	heat shock factor 1
HSR/PSR	heat-shock response/proteotoxic stress response
mTORC 1/2	mechanistic target of rapamycin complex 1/2
Proteostasis	proteome homeostasis
ROS	reactive oxygen species
SAPK/JNK	Stress-activated protein kinase/c-Jun NH(2)-terminal kinase
UPR	unfolded protein response

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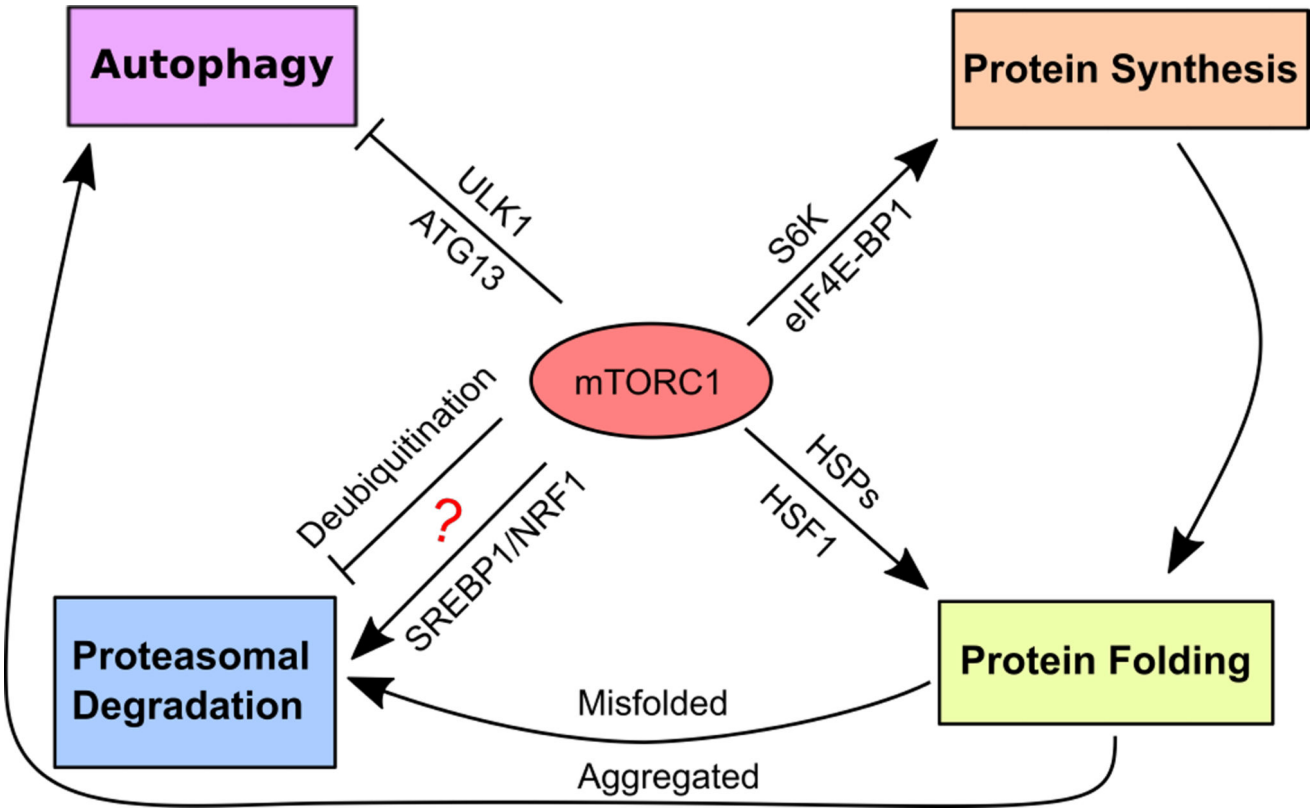

Figure 1. A key role of mTORC1 in proteostasis

While mTORC1 is widely recognized to control protein synthesis and autophagy, emerging evidence has implicated mTORC1 in regulating protein folding and proteasomal degradation as well. Thus, mTORC1 impacts all aspects of cellular proteostasis. The lines with an arrow head denote positive regulations. The T-bar lines denote negative or inhibitory regulations. The question mark denotes the controversial roles of mTORC1 in regulating proteasomal degradation. SREBP1: sterol regulatory element-binding protein 1.

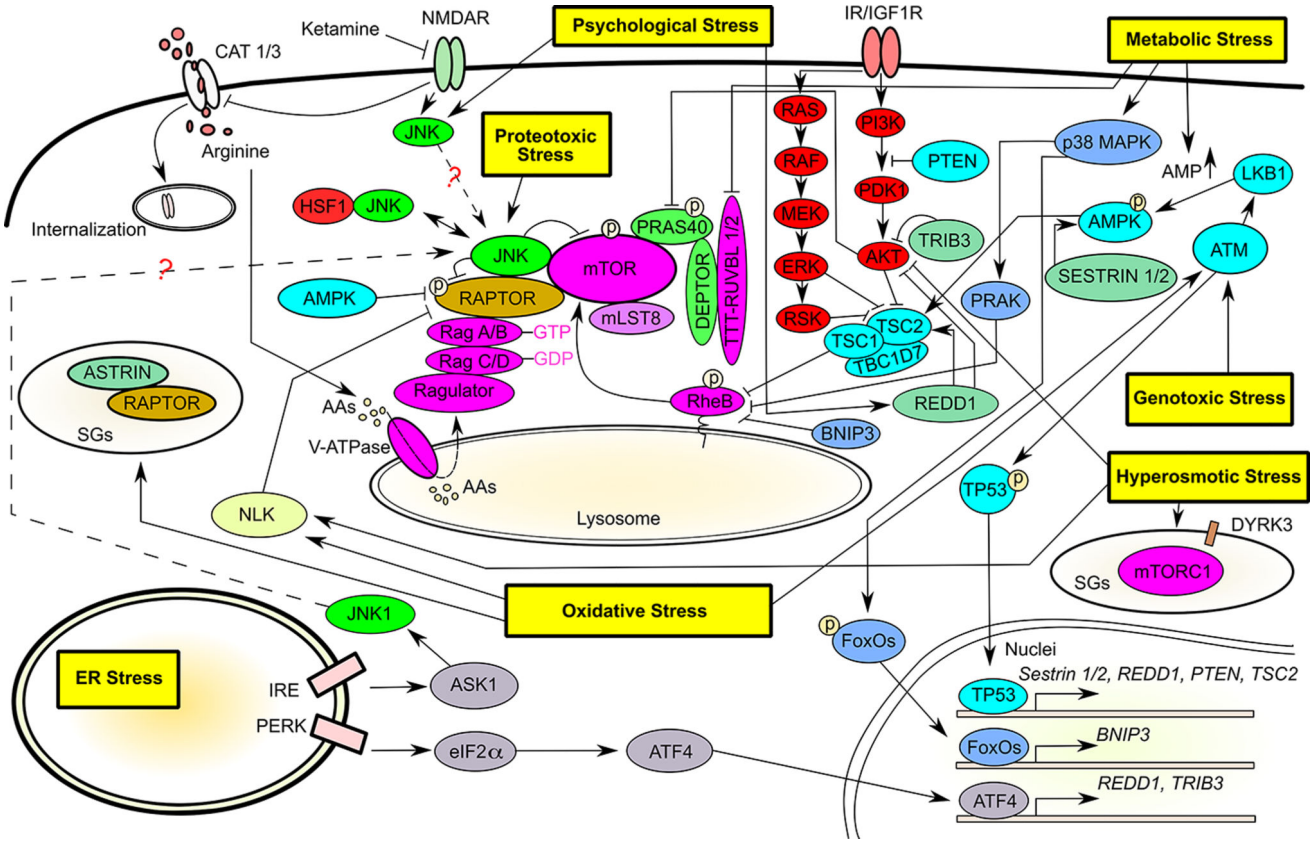

Figure 2. mTORC1 senses diverse stresses

The detailed molecular regulators are described in the main text. The question marks denote unexplored regulations. The objects in red represent oncogenes or pro-oncogenic factors; the objects in cyan represent tumor suppressors; and the objects in light green represent negative regulators of mTORC1. Within the mTORC1, the positive regulators are marked in purple and the negative regulators are marked in bright green. AAs: amino acids. AMP: Adenosine monophosphate. ASK1: apoptosis signal-regulating kinase. GTP: guanosine 5'-triphosphate. GDP: guanosine diphosphate. IR/IGF1R: insulin receptor/insulin-like growth factor 1 receptor. P: phosphorylation. PDK1: phosphoinositide-dependent kinase 1. SGs: stress granules.