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Protein synthesis is one of the most energy consuming processes in the cell. The mammalian/mechanistic target of rapamycin (mTOR) is a serine/threonine kinase that integrates a multitude of extracellular signals and intracellular cues to drive growth and proliferation. mTOR activity is altered in numerous pathological conditions, including metabolic syndrome and cancer. In addition to its well-established role in regulating mRNA translation, emerging studies indicate that mTOR modulates mitochondrial functions. In mammals, mTOR coordinates energy consumption by the mRNA translation machinery and mitochondrial energy production by stimulating synthesis of nucleus-encoded mitochondria-related proteins including TFAM, mitochondrial ribosomal proteins and components of complexes I and V. In this review, we highlight findings that link mTOR, mRNA translation and mitochondrial functions.

Keywords: 4E-BP1, eIF4E, mitochondria, metabolism, mRNA translation, mTOR, oxidative phosphorylation, TCA cycle

Background

Protein synthesis positively correlates with cell proliferation rates. It is therefore not surprising that upregulated mRNA translation is a common feature of pathological states that are characterized by aberrant proliferation including malignancies. In addition to playing an integral role in gene expression pathway, protein synthesis is one of the most energy consuming processes in the cell, and thus must be closely coordinated with cellular energy production. Similarly to protein synthesis, perturbations in energy metabolism are a frequent feature of cancer. These alterations in metabolic programs of cancer cells accommodate their elevated energy demand and provide building blocks (e.g., lipids, nucleotides) for continuous proliferation. Nonetheless, the mechanisms that coordinate mRNA translation and ATP production in mammals are still largely unknown.

The mechanistic/mammalian target of rapamycin (mTOR) is an evolutionarily conserved serine/threonine kinase that responds to a number of stimuli including hormones (insulin), growth factors (e.g., insulin-like growth factors [IGFs]), nutrients (amino acids), energy status, and oxygen levels to regulate cellular proliferation and growth rates. To bolster cellular proliferation and growth, mTOR stimulates anabolic processes including protein synthesis, and, as recent data show, acts as a major regulator of energy production in mitochondria. In turn, mTOR inhibits autophagy, which is a process that can eliminate mitochondria. As a consequence of inactivating mutations in tumor suppressor genes (e.g., PTEN, TSC1/2, NF1, LKB1) or hyperactivation of oncogenes (e.g., AKT, PI3K) mTOR signaling is upregulated in a
plethora of malignancies. Recently, numerous mTOR mutations that lead to its hyperactivation have been described in cancer. Upregulated mTOR activity is thought to play a central role in tumorigenesis and progression of a wide variety of cancers. Taken together, these findings suggest that mTOR is well positioned to act as a central node of cellular networks that coordinate mRNA translation and cellular energy production. Indeed, we have recently uncovered that mTOR coordinates protein synthesis and mitochondrial functions by selectively modulating synthesis of nuclear-encoded mitochondrial proteins.

**mTOR signaling pathway**

mTOR forms 2 distinct complexes, mTOR complex 1 (mTORC1) and 2 (mTORC2), which differ in their composition, downstream targets, and sensitivity to naturally occurring allosteric mTOR inhibitor rapamycin. mTORC1 stimulates protein synthesis and other anabolic processes to fuel cellular growth and proliferation, and is sensitive to acute rapamycin treatment. In most cell types, mTORC2 is insensitive to acute rapamycin treatment, regulates cytoskeletal organization, phosphorylates AGC kinases such as SGK1 and AKT, and has been implicated in the degradation of newly synthesized polypeptides.

A multitude of extracellular signals and intracellular cues have been implicated in the modulation of mTORC1 signaling. In response to growth factors, mTORC1 is activated via a PI3K/AKT pathway. AKT phosphorylates and inactivates tuberous sclerosis complex (TSC1/2), which acts as a GTPase-activating protein (GAP) toward the small GTPase RAS homolog expressed in brain (RHEB). Inhibition of TSCC2 to stabilize the TSC complex, leading to inhibition of mTORC1. mTORC1 activation leads to phosphorylation of a number of substrates including eukaryotic translation initiation factor 4E (eIF4E)-binding proteins (4E-BPs), ribosomal protein S6 kinases (S6Ks), LARP1, Atg13, ULK1/2, which results in the upregulation of anabolic processes such as protein and lipid synthesis and inhibition of autophagy (reviewed in ).

Compared to mTORC1, upstream regulation of mTORC2 is less well understood. mTORC2 kinase activity is stimulated by growth factors, seemingly through a PI3K-dependent association of mTORC2 with ribosomes. Growth factors (e.g. insulin) also induce mTORC2 localization to the mitochondria-associated ER membrane (MAM), a sub-compartment of the ER. There, mTORC2 controls MAM integrity and mitochondrial function in an AKT-dependent manner (see below).

**mTOR: a master regulator of mRNA translation**

mTORC1 stimulates protein synthesis by phosphorylating a plethora of substrates. The 2 best established effectors of mTORC1 signaling on protein synthesis are the eukaryotic translation initiation factor 4E (eIF4E)-binding proteins (4E-BPs) and ribosomal protein S6 kinases (S6Ks) (Fig. 1). eIF4E is a cap binding subunit of the eIF4F translation initiation complex that also comprises large scaffolding protein eIF4G and DEAD box helicase eIF4A and facilitates recruitment of mRNA to the ribosome. Phosphorylation of 4E-BPs by mTORC1 stimulates their release from eIF4E, which allows eIF4E:eIF4G association and the assembly of the eIF4F complex, thereby increasing translation initiation rates. S6Ks phosphorylate a number of components of the translational machinery and related regulators such as ribosomal protein S6, eIF4B, and PDCD4. mTORC1 has also been shown to phosphorylate additional components of the translation initiation machinery (e.g., eIF4G) and the eukaryotic translation elongation factor 2 kinase (eEF2K). Finally, mTORC1 is thought to increase translation by stimulating rRNA and tRNA synthesis, via activation of TIF-IA and inhibition of Maf1, respectively.

In addition to stimulating global protein synthesis, a large body of data indicate that mTOR selectively stimulates translation of a subset of transcripts including TOP mRNAs, which harbour a stretch of 4-14 pyrimidines following the cap structure, referred to as 5′ terminal oligopyrimidine (5′ TOP) motif. The vast majority of TOP mRNAs encode ribosomal proteins and other components of the protein synthesis machinery (e.g. eEF2). Albeit it has been initially thought that S6Ks mediate the effects of mTOR signaling on the synthesis of proteins encoded by TOP mRNAs, subsequent studies revealed that neither S6Ks nor phosphorylation of ribosomal protein S6 play a major role in regulating TOP mRNA translation. Two recent studies deployed high resolution translational profiling based on deep sequencing of ribosome-protected fragments to show that the effects of mTOR inhibitors on TOP mRNA translation are mediated by 4E-BPs. However, these results were challenged by a study showing that 4E-BPs are dispensable for the regulation of TOP mRNA translation under a variety of physiological stimuli including oxygen availability, amino acids and growth factors. These findings are consistent with a previous observation that eIF4E activity does not have a major influence on translation of TOP mRNAs. Therefore, the effects of mTOR signaling on TOP mRNA translation appear to be context dependent. To this end, additional factors including TIA/TIAR and LARP1 have been proposed to act as modulators of TOP mRNA translation.

In addition to regulating TOP mRNA translation, mTOR has been implicated in the regulation of synthesis of a number of cancer promoting proteins via inactivation of 4E-BPs and consequent increase in eIF4E activity. eIF4E exhibits oncogenic properties in vitro and in vivo and is overexpressed in the vast majority of cancers. These tumorigenic functions of eIF4E are a consequence of the selective upregulation of translation of mRNAs encoding cell cycle regulators (e.g., cyclins,
ODC), survival promoting proteins (Bcl-xL, survivin, osteopontin), pro-angiogenic factors (e.g. VEGF) and oncogenes (e.g., Myc, Pim1). These mRNAs are thought to be “eIF4E-sensitive,” as a majority of them bear long and highly structured 5’UTRs, rendering them more dependent on the unwinding activity of eIF4A helicase than those mRNAs that are characterized by short, unstructured 5’UTRs such as those encoding housekeeping proteins. eIF4A is recruited to mRNA as a part of the eIF4F complex, and its activity is significantly higher when it is part of the eIF4F complex than as a single protein. Therefore, increase in eIF4E availability is thought to selectively stimulates translation of those mRNAs that critically depend on the dissolution of 5’UTR secondary structures by eIF4A.

Using transcriptome-wide polysome profiling in conjunction with DNA microarrays, we demonstrated that, in addition to components of the translational machinery encoded by TOP mRNAs, mTOR inhibitors suppress the translation of transcripts encoding cell cycle and survival regulating proteins. Intriguingly, the most enriched mRNAs were those encoding for proteins implicated in the regulation of mitochondrial functions (Fig. 1).

Notwithstanding the fact that the precise mechanisms by which mTOR regulates protein synthesis are still being debated, these findings demonstrate that changes in mTOR activity are paralleled not only by quantitative, but also by qualitative changes in the pools of mRNAs that are being translated. Moreover, the effects of mTOR on selective changes in pools of translating mRNAs are likely to be dependent on the nature of the stimulus and mediated by different downstream effectors.

mTOR regulates mitochondrial mass and functions by coordinating multiple levels of gene expression

Emerging data indicate that, in eukaryotes, coordinated expression of genes that are involved in the same biochemical
processes is achieved via orchestration of different layers of gene expression machinery.75-77 Short-term (i.e. 12 h) mTOR inhibition does not induce major changes in the transcription of nuclear-encoded mitochondria-related genes.12 However, prolonged treatment with rapamycin downregulates the expression of pivotal transcriptional regulators of mitochondrial functions including PGC-1α, and ERR-α.78 This is paralleled by a decrease in mitochondrial respiration in skeletal muscle tissue and cell lines. The effect of mTOR on PGC-1α is mediated by ying-yang 1 (YY1), which belongs to the GLI-Kruppel class of zinc finger proteins and acts as a multifunctional transcriptional regulator.78 Depletion of YY1 results in downregulated expression of a number of nuclear encoded mitochondrial genes and decreased oxygen consumption.78 These findings suggest that, in addition to regulating the translation of nuclear-encoded mitochondria-related mRNAs, mTOR also regulates the transcription of nuclear encoded mitochondrial genes. Therefore, it appears that mTOR regulates the expression of nuclear-encoded mitochondrial genes by orchestrating their transcriptional and translational programs (Fig. 1). Moreover, it has been shown that mTOR directly governs the transcription of ERRα-target genes involved in energy metabolism including citric acid cycle and lipogenesis,79 further illustrating the coordination of transcriptional and translational energy homeostasis programs via mTOR.

mTOR links protein synthesis, mitochondrial function, and proliferation

Protein synthesis rates positively correlate with proliferation rates.1 In turn, mitochondrial ATP production is required to fuel protein synthesis and proliferation.6,7 These findings suggest that mitochondrial energy production, protein synthesis and proliferation are co-regulated, but the factors that orchestrate coordination of these processes are still largely unknown.

Experiments carried out in the model organism D. Melanogaster revealed that regulation of the expression of nuclear-encoded mitochondrial regulators at the level of translation plays a major role in lifespan extension by caloric restriction.80 Caloric restriction induces expression of d4E-BP (in contrast to mammals, flies express only one 4E-BP), which is paralleled by decreased phosphorylation of d4E-BP via downregulation of TOR signaling. Increased levels and decreased phosphorylation of d4E-BP resulted in suppression of global protein synthesis, but increased the translational efficacy of mRNAs encoding factors implicated in mitochondrial respiration.80 Although the precise mechanism underpinning the upregulation of the translation of mitochondria-regulating mRNAs under dietary restriction is unknown, these findings put forward a model whereby nutrient deprivation selectively induces the synthesis of mitochondrial regulators that impact the function of the electron transport chain via downregulation of TOR and activation of d4E-BP.

In mammalian cells, however, mTORC1 stimulates the synthesis of a number of nuclear-encoded mitochondrial regulators such as TFAM, mitochondrial ribosomal proteins and components of complex I and V by upregulating the translation of corresponding mRNAs.12 (Fig. 1). Inhibition of mTOR signaling strongly decreases mitochondrial biogenesis and respiration in 4E-BP proficient cells, but not in those lacking 4E-BPs.12 The elevated mitochondrial respiratory capacity observed in cells where mTORC1 is hyperactivated by PTEN loss also appears to be mediated by the selective upregulation of expression of components of the electron transport chain via inactivation of 4E-BPs.81 In wild-type mice, mTOR inhibitors cause reduced systemic oxygen consumption and decreased locomotor activity and heat production. Mice lacking 4E-BPs were resistant to the systemic effects of mTOR inhibitors.12 Notwithstanding the apparent differences in the effects of the TOR/4E-BP pathway on translation of mRNAs encoding mitochondrial regulators in flies and mammals that likely stem from their different metabolic requirements, these findings indicate that TOR and 4E-BPs play a major role in coupling mitochondrial functions and translation. Moreover, it seems that translational control may play an even broader role in the regulation of mitochondrial functions, in as much as Largen, which is an important regulator of cells size, impacts mitochondrial activity by inducing selective perturbations in the translation of nuclear-encoded mitochondria-related mRNAs in a mTOR-independent manner.82 Collectively, these studies show that translational activity in the cell influences mitochondrial functions.

In addition to regulating synthesis of nuclear-encoded mitochondrial regulators, the mTORC1/4E-BP pathway regulates translation of mRNAs that encode proteins that promote proliferation such as cyclins, ODC, and Myc.74 Accordingly, 4E-BP status in the cell is a major determinant of the effects of mTOR on proliferation, inasmuch as cells lacking 4E-BPs maintain their proliferation under circumstances where mTORC1 signaling is inhibited by pharmacological (e.g. active-site mTOR inhibitors) or genetic (depletion of raptor) means or by nutrient deprivation (e.g., serum or amino-acid depletion).83 These results suggest that mTOR coordinates mitochondrial functions and proliferation, at least in part by modulating translation programs (Fig. 1).

In addition to mTORC1, mTORC2 appears to be an important regulator of mitochondrial functions (Fig. 1). Upon growth factor stimulation mTORC2 is recruited to the mitochondria-associated ER membrane (MAM), where it maintains MAM integrity via AKT dependent phosphorylation of MAM resident proteins including IP3 receptor and hexokinase 2.35 Loss of mTORC2 activity leads to disruption of MAM, paralleled by increase in mitochondrial membrane potential, and calcium uptake.35 This suggests that mTORC1 and mTORC2 play distinct, non-overlapping roles in regulating mitochondrial functions.

mTOR coordinates mRNA translation, availability of cellular building blocks and autophagy

mTORC1 promotes synthesis of building blocks that are required for cell proliferation (Fig. 1). To this end, mTORC1 stimulates lipid and sterol synthesis by activating sterol regulatory element-binding proteins (SREBPs),84 whereas it negatively regulates β-oxidation of free fatty
acids. In vivo, depletion of raptor in adipose tissue of mice induces a lean phenotype, paralleled by increased energy expenditure and increased levels of mitochondrial uncoupling proteins. In addition, mTORC1 stimulates nucleotide synthesis via induction of the pentose phosphate pathway and S6K-mediated activation of carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, dihydroorotase (CAD). Analogous to enhancing mitochondrial functions by selectively increasing mRNA translation, mTORC1 appears to link protein synthesis and nucleotide availability inasmuch as eIF4E stimulates nucleotide synthesis via increased translation of phosphoribosylpyrophosphate synthetase 2 (PRPS2) mRNA. Increased aerobic glycolysis and glutaminolysis are hallmarks of energy metabolism reprogramming in cancer. mTORC1 increases glucose uptake and glycolysis through induction of the hypoxia-inducible factor 1α (HIF1α). In addition, mTORC1 pathway stimulates glycolamine anaplerosis and cell proliferation by repressing SIRT4 and thus promoting the activity of glutamate dehydrogenase. mTORC2 has also been shown to play a major role in the regulation of energy metabolism. For instance, liver-specific inhibition of mTORC2 signaling in conditional rictor knock-out mice revealed that mTORC2 regulates glycolysis and lipid metabolism through the Akt-dependent activation of glucokinase and SREBP1c, respectively.

In parallel to stimulating anabolic processes, mTOR also inhibits autophagy (Fig. 1), which is a major catabolic process in the cell. mTORC1 inhibits autophagosome formation by phosphorylating the pro-autophagic kinase ULK1 and thus preventing its activation by AMPK, and by phosphorylating and inhibiting ATG13, a positive regulator of ULK1. mTORC1 also inhibits autophagy indirectly by blocking lysosome biogenesis through the phosphorylation and inhibition of the nuclear translocation of transcription factor EB (TFEB). mTORC1 inhibition by aTORi reduces mitochondrial mass by induction of autophagy, and these effects were alleviated by suppressing autophagy via depletion of ATG5. Therefore, mTORC1 induces mitochondrial biogenesis and functions by orchestrating synthesis of nuclear-encoded mitochondrial regulators and inhibiting autophagy.

Conclusions

mTOR activity is central to energy homeostasis, inasmuch as it coordinates protein synthesis, cell growth and proliferation, generation of metabolic intermediates, and mitochondrial biogenesis and functions (Fig. 1). Accordingly, dysregulation of mTOR signaling and mitochondrial dysfunction underpin aging and diseases such as cancer, diabetes, and neurodegeneration (reviewed in ). For instance, increased life span of female transgenic mice expressing non-steroidal anti-inflammatory drug-activated gene (NAG-1)/GDF15 is paralleled by down-regulation of mTOR activity. Interestingly, many components of the electron transport chain (ETC) complexes that show alteration in expression in the process of aging, such as NDUF6, ATP5D, ATP5L and ATP5O, were shown to be translationally controlled by mTOR. Cancer is characterized by aberrant proliferation, increased protein synthesis and perturbations in cellular energy metabolism. In turn, mTOR signaling is dysregulated in a vast majority of cancers, while low expression and high phosphorylation status of 4E-BPs, as well as upregulation in eIF4E levels, are also common in neoplasia. Notably, increase in eIF4E/4E-BP ratio appears to be a major mechanism of resistance to PI3K and mTOR-targeted therapies. This raises an intriguing possibility that cancer cells hijack mechanisms by which the hyperactivation of the mTOR/4E-BP/eIF4E pathway coordinates mitochondrial functions, nucleotide and lipid synthesis and translational programs to fuel neoplastic growth. A recent study established a mTOR-independent link between protein synthesis and mitochondrial functions, whereby Largen appears to regulate cell growth at least in part by modulating translation of nuclear-encoded mRNAs that code mitochondrial proteins in rapamycin-insensitive manner. Although the underlying mechanisms of this phenomenon remain to be established, these findings suggest that multiple pathways evolved to maintain cellular energy balance by coordinating mitochondrial functions, translational activity, cellular growth and proliferation. Therefore, the identification of specific translational programs mediated by mTOR-dependent and -independent pathways, their effectors, and the mechanisms by which they modify mitochondrial functions represent a promising avenue to improve the understanding of the molecular mechanisms of cellular energy homeostasis that contrast normal and malignant cells.

Acknowledgments

We are thankful to Shannon McLaughlan for technical support and Valentina Gandin for invaluable comments.

Funding

This perspective is based on research projects in St-Pierre and Topisirovic labs that are supported by a Terry Fox Research Institute team grant (TFF-116128) to I.T., M.P. and J.S-P. and grants from the Canadian Institutes of Health Research (CIHR MOP-115195 to LT; MOP-106603 to J.S-P.). I.T. is a recipient of CIHR New Investigator Salary Award. J.S-P. is an FRQS scholar. M. M. is a recipient of a CIHR-funded Chemical Biology Postdoctoral fellowship and Canadian Diabetes Association Postdoctoral fellowship.

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