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Review Article

Regulation of cellular anabolism by mTOR: or how I learned to stop worrying and love translation

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ABSTRACT

The process and regulation of cellular metabolism are extremely complex and accomplished through multiple signalling pathways that operate in parallel, and often experience significant overlap in upstream and downstream a signal transduction. Despite this complexity, single pathway or even single protein activations are commonly used to extrapolate broad characterizations of cellular metabolism. Furthermore, multiple routes for peptide-chain translation initiation exist, some of which may be either exclusive or overlapping depending on the state and environment of the cell. While it may be highly impractical to account for every aspect of metabolic regulation and permutation of mRNA translation, it is important to acknowledge that investigations relating to these pathways are often incomplete and not necessarily indicative of the overall metabolic status. This becomes urgent when considering the role that cellular anabolism plays in both healthy cellular functions and the aetiology of several disease's altered metabolisms. This review describes recent advances in the understanding of cellular metabolic regulation, with specific focus given to the complexity of 'downstream' mRNA translation initiation through both mTOR-dependent and mTOR-independent signallings.

Introduction

Over the past 15 years, great strides have been made in describing the complex mechanisms that regulate growth in eukaryotic cells. Often, at the centre of these discussions is the mechanistic target of rapamycin or mTOR. This protein and its associated complexes sit at a focal point of anabolic and catabolic regulations. mTOR is responsible for regulating many aspects of growth in the cell by integrating the input from a number of upstream signals such as nutrient availability, energy status, inflammation, genotoxic stress, oxidative stress, and multiple growth factors.[1–6] There also exist a number of signalling cascades that can occur parallel to canonical mTOR signalling, with some of them being regulated independently of mTOR but able to affect similar downstream metabolic changes.[7–13] While we acknowledge 'upstream' signal transduction leading to the activation of the anabolic apparatus, the purpose of this review is to describe in detail the 'downstream' role of mTOR-dependent and -independent signalling pathways in the regulation of cellular metabolism, with a focus on mRNA translation initiation due to its considerable control over the ultimate endpoint of cellular protein expression.

Traditional view of mRNA translation

Our understandings of the mechanisms regulating mRNA translation, or protein synthesis, have been constantly evolving since the discovery of mRNA and polysomes in the 1960s. One area of research that has gained popularity in recent years is that pertaining to the control of non-canonical methods of protein synthesis. The traditional view of mRNA translation has involved a very strict environment of upstream signalling emanating from or arising through the mTOR kinase, ultimately leading to the activation of specific initiation factors; the ribosomal binding to the mRNA mediated through the 7-methylguanosine cap (m7G) and eIF2; the subsequent scanning for an AUG start codon downstream from an appropriate Kozak sequence, and the binding of the methionine initiator tRNA (Met-tRNAi) to begin the translational process.[14–16] While these steps represent a standardized dogma, our current understanding of

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translation initiation now includes alternative processes for each of these previously mentioned steps.

mTOR structure and function

A central feature of anabolic regulation involves the mTOR kinase. mTOR was formally discovered in 1994 by three independent laboratories, namely Stuart L. Schreiber, David M. Sabatini, and Robert T. Abraham.[17–19] However, a *target of rapamycin* has been known to exist in some form/forms since the discovery of Rapamycin from soil bacterium on Easter Island in the 1960s.[20] Since that time, mTOR has been afforded much scientific inquiry. mTOR exists in mammalian cells as a 289 kDa serine/threonine protein kinase of the PI3K-related Kinases (PIKK) family, and forms three distinct protein complexes known as mTOR complex 1 (mTORC1), mTOR complex 2 (mTORC2) and the recently discovered mTOR complex 3 (mTORC3).[5,21,22] Although the mTOR kinase is the common feature among all three, these protein complexes differ in their binding partners, upstream input, and downstream targets.

The mTORC1 configuration is defined by its interaction with the regulatory-associated protein of mTOR (RAPTOR), a scaffolding protein that is critical to mTOR's subcellular localization to the lysosome and in mediating mTOR's interaction with other mTORC1 associated subunits.[5,23] RAPTOR also mediates the interaction of the proline-rich AKT substrate 40 kDa (PRAS40) endogenous mTORC1 inhibitor. mTORC2 is defined by its interaction with the rapamycin-insensitive companion of mTOR (RICTOR), which may aid in mTOR's subcellular localization to the plasma membrane, and in mediating mTOR's interaction with other mTORC2-associated subunits.[5,24] RICTOR also mediates the binding of the MAPK-interacting protein 1 (mSIN1), which may aid in mTORC2 interactions with the plasma membrane [25]. Both complexes contain the mammalian lethal with SEC13 protein 8 (mLST8), which appears to stabilize the kinase domain of both complexes, and removal of this protein inhibits the structure and function of mTORC2, while mTORC1 downstream substrates appear to remain unaffected.[5] In both of these complexes, mTOR directly interacts with an inhibitory protein, DEP-domain containing mTOR-interacting protein (DEPTOR), and plays a critical role in the regulation of both mTOR complexes through multiple complex feedback mechanisms that are only partially understood.[26–30] The mTORC3 complex was only recently discovered, and very little is known about its downstream targets or its binding partners beyond ETV7, a transcription factor commonly upregulated with many types of cancer.[21]

While each of the mTOR complexes responds to different inputs and has unique downstream targets, these functions are much better defined for mTORC1 than mTORC2, and we know considerably more about mTORC2 when compared to mTORC3. mTORC1 is sensitive to signalling input along the IRS-1/PI3K/AKT signalling axis, and is responsible for the regulation of a number of critical cellular functions including protein synthesis, lipid synthesis and catabolism, nucleotide synthesis, energy homeostasis, autophagy, mitochondrial biogenesis, and mitochondrial metabolism.[4–6,31] In contrast, mTORC2 appears to play important roles in the organization of the cellular cytoskeleton, and in complex interactions with AKT that may serve to reinforce cross-talk between mTORC1 and mTORC2, but our understandings of these relationships are far from complete.[32]

DEPTOR

One of the more interesting and understudied mTOR complex components is a protein known as DEPTOR, which is an endogenous inhibitor of mTOR, regardless of complexity, through direct binding to the mTOR kinase. While DEPTOR is bound to mTOR, the mTOR kinase exhibits reduced kinase activity as measured through the phosphorylation of downstream targets, and DEPTOR depletion leads to a promotion of mTORC1 activity.[28,30] Through a complex relationship, DEPTOR and mTOR reciprocally inhibit each other, generating double-negative feedback loops (18). Once mTOR is activated via upstream signalling, it is able to phosphorylate the bound DEPTOR protein, triggering its release from mTOR.[27,33] This enables the subsequent phosphorylation of DEPTOR by the constitutively active Casein Kinase I (CKI), and ultimately the ubiquitination and degradation via the $SCF^{\beta-TRCP}$ E3 ubiquitin ligase complex in a β-TRCP dependent fashion.[27,33] This DEPTOR degradative process is dependent upon mTOR activation and the availability of $SCF^{\beta-TRCP}$ complex, as the initial phosphorylation event may not be sufficient to remove the inhibitory effect of DEPTOR on mTOR but serve to enable further protein modifications by CKI and β-TRCP. This process generates an auto-amplification loop where mTOR is able to promote its full activation through the initiation of DEPTOR degradation.[27]

In some contexts, DEPTOR can act as an oncogene, and in others, a tumour suppressor.[26,30] Some have speculated that in some cases, increased DEPTOR levels can relieve the negative feedback from p70 S6 kinase on IRS-1, allowing for increased signal transduction through the IRS/AKT/mTOR signalling axis.[34] Decreased DEPTOR levels would simply allow for a lower threshold of upstream signal to activate mTOR and therefore downstream anabolic targets. This presents a complicated relationship, which is compounded by the fact that each of the mTOR complexes appears to compete for DEPTOR binding, with RAPTOR being a preferred binding partner than RICTOR.[30] Varusai et al. indicated that there may be a "therapeutic window" of DEPTOR overexpression that can serve to suppress mTORC1/2 activation, while also inhibiting AKT activation.[35] In addition, they also indicated that the stability of the rapidly changing system is improved with longer timescales, and are ultimately dependent upon the rate of synthesis and degradation of DEPTOR.[35]

Changes in the capacity of a cell to express DEPTOR protein have been reported in some studies as a potential causative factor for altered anabolic signalling,[28] while others have suggested that these outcomes could be a consequence of changes in mTOR activity, ultimately leading to changes in the expression of DEPTOR.[34] Caron et al. noted in a comprehensive review that reductions in DEPTOR protein are generally a direct result of mTOR activation, as opposed to reductions in DEPTOR protein allowing for increases in mTOR activation.[34] While both arguments have merit, due to the complexities of the interaction between these two proteins, the positive and negative feedback loops associated with this pathway, and the fact that mTOR's activation could play an important role in the translation of DEPTOR mRNA, it seems difficult to assess this cause and effect relationship without the stable and long-term overexpression of DEPTOR protein, independent of mTORC1/2's significant role in reducing DEPTOR expression when activated. This sentiment is mirrored by Caron et al., stating that DEPTOR silencing or overexpression is likely required to determine the true effects of any treatment on anabolic signalling through DEPTOR-mTOR.[34]

Protein synthesis

Within eukaryotic cells, messenger RNA (mRNA) is translated into proteins via several independent but overlapping processes. The translational process employed by the cell is largely dictated by the mRNA characteristics that determine which pieces of cellular machinery are required to take part in peptide-chain initiation, translation, or termination, but can also be defined by the subcellular compartment in which it takes place (e.g. the mitochondria). In addition to differences in cellular machinery, these specific translational processes can be subject to drastic differences in regulation and control that not only influence the ultimate rate of protein synthesis within the cell, but also determine the type of mRNAs that will be prioritized for translation. From subtle differences in transcripts due to the heterogeneity of transcription start sites, to the vast differences in 5′ UTR sequence and secondary structure, the manufacture of a given protein is regulated post-transcriptionally based on the configuration of the mRNA and/or the specific translational processes available at the time.[14,36,37] Aside from the energy status of the cell, translation initiation is widely considered to be the rate-limiting step for protein synthesis and is a critical control point to

determine not only what transcripts have access to the anabolic apparatus, but their affinity to anabolic machinery and the ease by which they are translated. All protein-coding transcripts within eukaryotic cells fall under two overlapping categories: Cap-Dependent (CD), and Cap-Independent (CI).[14] Previously thought to only occur during times of great cellular stress, CI translation of particular mRNA transcripts is now believed to occur simultaneously with CD translation in virtually all eukaryotic cells, albeit with notable differences in priority and efficiency depending on the nature of the specific transcript.[36] Classically categorized by their dependency on 7-methylguanosine cap (m7G) binding initiation factors, many of these transcripts are now known to exhibit properties of both classifications and can take part in translation through a variety of processes, under a variety of conditions.[10,38] One such mRNA is that of mTOR, possessing both CD and CI elements, ensuring that it can be translated under normal conditions and during times of great cellular stress.[10] However, CI transcripts are likely largely unidentified due to the dramatic variations in the 5' UTR primary and secondary structure that play an important role in their translation.[10] Identifying and quantifying the contribution of CD and CI translation initiation to overall protein synthesis, and the synthesis of specific proteins will be of the utmost importance in developing a complete understanding of the human translatome.

Basic overview

From the most basic perspective, protein synthesis is the process of converting mRNA transcripts into useable proteins within the cell. Generally, it is described as being a three-part process, consisting of initiation, elongation, and termination. Each of these steps is carried out by complex ribonucleoproteins consisting of 80 different proteins and four RNA molecules that form the different subunits comprising a fully formed ribosome. The exact composition and size of the ribosomal subunits will depend upon the location of translation, but there are always two ribosomal subunits, one large, and one small. If the translation is occurring in the cytosol, the small (40S) subunit and the large (60S) subunit together form the 80S ribosome.[37]

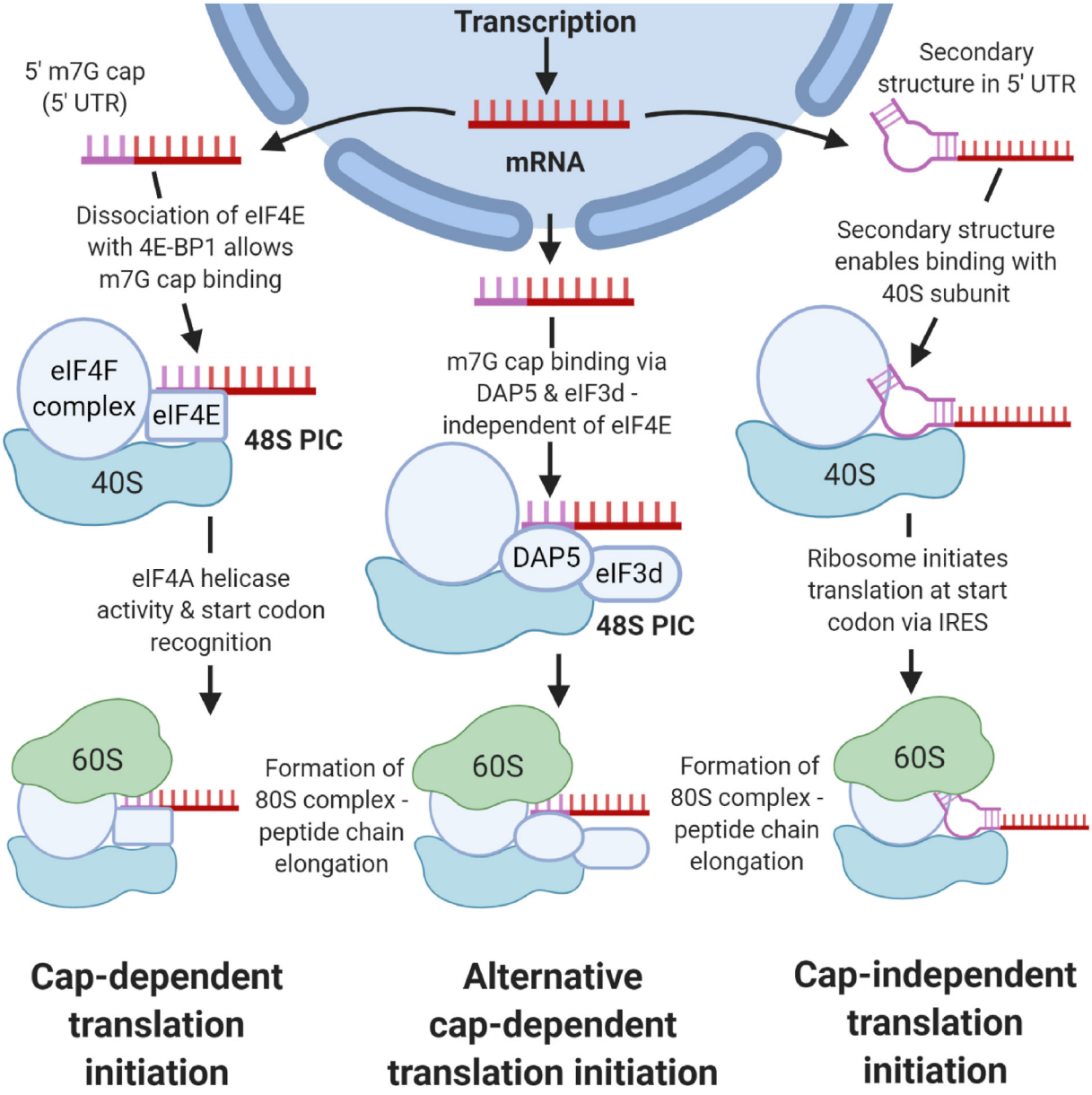

Fig. 1. Multiple avenues of mRNA translation in eukaryotic cells.

In addition to the location within the cell, different types of translation can occur based on the sequence and secondary structure of mRNA transcripts. Not only do these different mechanisms of translation operate through different collections of the translational machinery, they occur at different efficiencies, are subject to different upstream signalling input, and are ultimately responsible for the translation of specific subsets of mRNA transcripts within the cell (Fig. 1).

Cap-dependent translation initiation

The most common type of translation that takes place in eukaryotic cells is known as cap-dependent (CD) translation and is so named due to the sequence and structure of the 5' untranslated region (UTR) of this class of transcripts. Specifically, the 7-methylguanosine cap (m7G) of CD transcripts requires the binding of eukaryotic initiation factor 4E (eIF4E) as part of the eukaryotic initiation factor 4F (eIF4F) complex, to enable the mRNA to interface with the 40S small ribosomal subunit, to form the 43S preinitiation complex (43S PIC).[14] For eIF4E to be made available, 4E-binding protein 1 (4E-BP1) must be deactivated through phosphorylation to cause dissociation with eIF4E. Of the four relevant 4E-BP1 phosphorylation sites, mTORC1 is known to phosphorylate Thr 37 and Thr 46, which is not independently sufficient to release 4E-BP1 from eIF4E, but rather appears to prime 4E-BP1 for phosphorylation at Ser 65 and Thr 70.[39] It is believed that phosphorylation at Ser 65 and Thr 70 may be required for full deactivation and complete dissociation from eIF4E, although the specific kinase responsible for this phosphorylation is unknown, some sources point to mTOR or an mTOR complex-associated protein.[40]

All mRNA within a normal, healthy cell contains a 7-methylguanosine cap (m7G) at the 5′ end that facilitates interaction with eukaryotic initiation factor 4E (eIF4E), which ultimately allows for coupling of the mature transcript with the small ribosomal subunit as part of the 43S preinitiation complex (PIC).[14] This new complex consisting of the 43S PIC and transcript form the 48S PIC. The binding of eIF4E to the 5′ m7G cap structure is generally considered to be the overall rate-limiting step of translation under most circumstances. Due to binding at the cap structure, often significantly upstream from a start codon, ATP-dependent eIF4A helicase is required to unwind any secondary structures present in the downstream 5' untranslated region (UTR) to enable efficient scanning for an appropriate start codon (generally AUG) within a Kozak sequence.[41] When the appropriate start codon is encountered, the methionine tRNA initiator (Met-tRNAi) anticodon in the ribosomal P site, binds to the mRNA start codon, facilitated by eIF5 in the PIC by hydrolyzing a GTP bound to eIF2.[14] This is marked by a conformational change in the PIC, enabling it to bind to the 60S large ribosomal subunit to form the 80S ribosomal complex and enter the elongation phase of protein translation.[14]

As the 80S ribosomal unit moves along the transcript during the elongation phase, newly formed 40S subunits, guided by eIF4e, can bind to the 5' m7G cap, and begin scanning for a start codon.[14] These mRNA with multiple ribosomal units engaging in the simultaneous translation are referred to as polysomes.

5' TOP mRNA

There is a subset of CD transcripts that encode many of the growth-related proteins, including many of the translation factors and nearly all ribosomal proteins, which contain a 5′ terminal oligopyrimidine (5′ TOP) motif. LARP1 was recently shown to be involved in the binding of these specialized 5′TOP mRNAs in an mTORC1 activation-dependent manner.[12] LARP1 associates with mTORC1 via RAPTOR, and upon mTORC1 inhibition, is liberated and able to bind 5′TOP mRNA to repress their expression.[7] This interaction occurs competitively with eIF4E but may occur alongside eIF4A, and likely eIF4G.[12] In addition, LARP1, in conjunction with the poly-A binding protein (PABP) and eIF4G, is able to bind to the 40S ribosomal subunit, by creating an alternative "48S"-like complex that is able to stabilize the 5′TOP mRNA, but not allowing for its expression.[8] This indicates a dynamic relationship between mTORC1 activity and the preferential expression of critical components of the anabolic machinery required to translate mRNA into proteins. This ultimately serves two purposes. Firstly, the cell is able to preferentially halt the expansion of anabolic machinery very quickly upon mTORC1 inhibition, and secondly, is able to preserve the mRNA coding for the same anabolic machinery through a stabilizing complexation through LARP1 in the face of halted anabolism. In addition to LARP1, there have been a number of mRNA cap-binding proteins identified that have opened the door to the possibility of further sub-classifications of mRNA that may receive preferential treatment during translation.[12]

Alternative cap-dependent translation initiation

In roughly 20% of CD mRNAs, eIF4E is not required to initiate translation, but is done in a way that still requires the 5′ cap structure. DAP5, an eIF4GI homologue, can utilize eIF3d to facilitate direct binding of the PIC to the 5' m7G cap to enable translation initiation independently of eIF4E availability or 4E-BP1 activation through mTORC1.[42] These transcripts do not contain CI internal ribosome entry site elements (IRES), although DAP5 is capable of promoting the translation initiation of a fair number of mRNAs containing IRESs as well.[42] Genome-wide translation profiling has revealed that DAP5 is critically important in the CI (IRES-mediated) translation of proteins involved in cell differentiation, cell cycle progression, apoptosis, and metastasis, including Bcl-2, Apaf-1, cIAP1, CDK1, and p53 (3). Interestingly, the genome-wide transcriptome and translatome profiling revealed highly DAP5-dependent mRNAs involved in many cell functions, including cell death, cell proliferation, cell mobility, DNA damage and repair, and translation initiation, that do not contain IRES elements, and are translated in a CD, but eIF4E independent fashion. The authors report that the translation of roughly 20% of all mRNAs was found to be highly dependent on the expression of DAP5 and eIF3d.[42] While this mechanism occurs independently of eIF4E canonical cap-binding, it is still entirely dependent upon cap-binding processes and is therefore still technically CD.

Cap-independent translation initiation

In contrast to the eIF4E CD mechanisms described above, cap-independent (CI) translation occurs independently of m7G cap binding, and instead relies upon the presence of 5′ or 3′ UTR elements that directly interface with elements of the translation apparatus. This subset of translation initiation is extremely varied, and poorly defined when compared to CD translation initiation. The recruitment of mRNAs to the 40S ribosomal subunit using a CI process can occur through the direct binding of specialized mRNA sequences directly to ribosomal subunits or translation initiation factors, including DAP5 and eIF4GI.[14,37,43] These specialized mRNA sequences often feature complex secondary RNA structures in the 5′ and/or 3′ UTRs of certain transcripts. Many of these sequences enable the direct binding of the 40S subunit just upstream or directly at the start codon sequence via specific internal ribosome entry site (IRES) elements.[44] In some mRNAs, specifically under apoptotic conditions, translation can occur through a 5' end-dependent scanning mechanism, in what is known as a CI translational enhancer (CITE). Transcripts that contain these CI regions are often related to growth, programmed cell death, and stress response, including many that have been classified as oncogenes.[37]

It should be noted that these CI motifs containing mRNAs also contain an m7G cap, as are all cellular RNA polymerase II-transcribed mRNAs.[45] Therefore, transcripts that contain both CD and CI elements can be translated through multiple independently regulated mechanisms. Although the importance of why a transcript would contain both CD and -independent sequence motifs is not completely understood, it suggests that mRNA translation by one mechanism or the other is largely dependent on whether mTORC1 is on or off.[10] In other words, although CI

translation does not require mTORC1 activity, translation may largely occur for those transcripts only when mTORC1 is not active, as elevated activity of mTORC1 may preferentially direct CD sequences to the anabolic apparatus at the expense of the available CI transcripts. Alternatively, having CI sequences may allow for translation of those transcripts whether mTORC1 is active or not. As noted earlier, one such transcript is the human mTOR transcript.[10] It's 5′ UTR forms a highly folded RNA scaffold that enables it to bind to the 40S subunit with high affinity, thereby enabling some basal amount of mTOR mRNA translation regardless of upstream signalling conditions within the cell.[10] While CD translation is never completely halted, the affinity of the translational machinery towards particular mRNA elements can be dramatically altered.[44] Having both CD and -independent translation sequences may be critical for the progression of certain phases of the cell cycle, and the maintenance of normal cellular functions under various stress conditions.

Anabolic regulation

Historically, the regulation of anabolism, including protein synthesis, has fallen under two distinct categories that define their signalling pathways: rapamycin-sensitive, and rapamycin-insensitive.[21,46–48] The former refers to signalling pathways that converge on mTORC1 (including insulin-sensitive IRS-1/PI3K/AKT signalling, energy sensitive AMPK signalling, amino acid-sensitive signalling through GATOR1/2, and mechanotransduction signalling through PLD1 mediated phosphatidic acid (PA) production), while the latter refers to all other signalling that is independent of the rapamycin-induced inhibition of mTORC1. We should note, however, that this nomenclature has been revised somewhat, as mTORC1 phosphorylation of 4E-BP1 at Thr46 is sufficient to prevent some level eIF4E:4E-BP1 binding and can occur in a rapamycin-insensitive manner.[48] The differential response of mTORC1 toward downstream substrates in the presence of rapamycin has been attributed to differences in substrate "quality" as measured by their affinity for the mTORC1 kinase under varying circumstances.[49]

Each of the mTOR complexes is subject to multiple regulatory mechanisms that range from upstream signal transduction, self-limiting inhibition, and downstream negative feedback through changes in both transcription and translation of mTOR interacting proteins. As the aptly named target of rapamycin, mTORC1 is inhibited by direct binding of the rapamycin/FKBP12 complex to mTOR and subsequent allosteric inhibition of mTORC1's kinase domain.[4,5,50,51] However, mTORC2 is not subject to direct binding by the rapamycin/FKBP12 complex, and as a result, not acutely impacted by treatment with rapamycin. Rather, the long-term treatment of rapamycin ultimately influences mTORC2 activity through alterations in feedback from the direct inhibition of mTORC1[52], as well as through the inhibition of mTORC2 complex formation by sequestering rapamycin-bound mTOR that cannot form new mTORC2.[5,52,53] Although upstream activation of mTOR is not the focus of this review, the complexity of this activation is intensely investigated (Fig. 2).

mTOR independent, but cap-dependent anabolism

The Ras/Raf/MEK/ERK signalling pathway can be activated alongside the IRS-1/PI3K/AKT/mTOR pathway, but can also act independently, while still influencing the activity of some of the same downstream effectors. Broadly, this pathway can be activated by a variety of extracellular stimuli occurring through G-coupled protein receptors and receptor tyrosine kinases (including the insulin receptor, and various integrin transmembrane receptors). Once activated, this signalling pathway plays an important role in the regulation of the cell cycle, apoptosis, growth, and cellular differentiation.

When an extracellular mitogen or growth factor binds and activates an appropriate membrane receptor, the small GTP binding protein, Ras, is liberated from its bound GDP molecule, allowing it to bind to a new

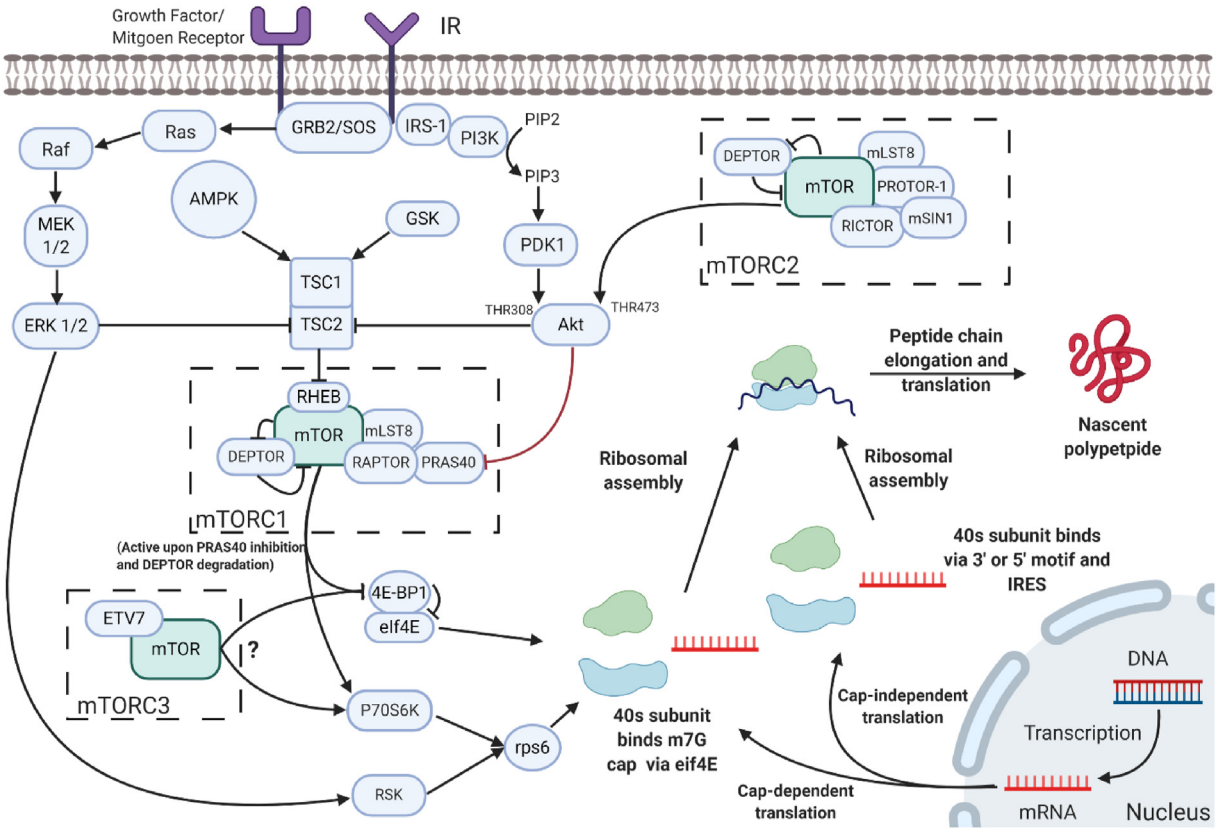

Fig. 2. mTOR complex signaling.

GTP. This activated form of Ras, is capable of hydrolyzing the bound GTP to recruit and phosphorylate multiple downstream targets, including the protein kinase Raf. Raf is then able to promote the activity of MEK1/2 protein kinases through the phosphorylation of serine/threonine residues, which are ultimately responsible for the phosphorylation and activation of ERK1/2. The ERK1/2 proteins are responsible for the phosphorylation of at least 160 downstream targets, including various transcription factors and cytosolic signalling enzymes.[54] Of particular note is the downstream target RSK (ribosomal S6 kinase), which then activates ribosomal protein S6 (exclusively through phosphorylation of $Ser^{235/236}$) a component of the 40S ribosomal subunit, leading to its recruitment to the m7G cap structure, and the formation of the 43S pre-initiation complex required for CD translation.[11] This can occur cooperatively and/or independently of the activation of p70S6 kinase by the rapamycin-sensitive mTORC1 pathway.

Dysregulation and disease

While metabolic dysregulation is associated with many human diseases, it is not always clear if the dysregulation in a certain tissue is driving the progression of the disease, or if the dysregulation is a byproduct of cellular attempts at homeostasis in the face of abnormal extracellular conditions. In some cases, this relationship is fairly straightforward. However, oftentimes the distinction between the two can give insight into the origins of the pathology. In many human cancers, a single mutation can lead to a myriad of cellular signalling dysregulation that can have lethal effects. These mutations can have dramatic effects on upstream signalling through the IRS-1/PI3K/AKT/mTOR signalling axis (for reviews on upstream signalling, see Liu & Sabatini 2020; see Fig. 2).[5] In fact, in most human cancers, DEPTOR expression is low,[30] and in some cancers, DEPTOR downregulation is an indicator of poor prognosis.[55] It is not clear if the upstream dysregulation and loss of DEPTOR favour either a cap-dependent or –independent process for anabolism.

On the other hand, some neurodegenerative diseases can be characterized by disrupted anabolic or catabolic signalling, with some occurring in mTOR-dependent signalling pathways. For example, the accumulation of amyloid-β plaques in the precentral gyrus, postcentral gyrus and occipital lobe of Alzheimer's patients has been associated with a marked decrease in DEPTOR protein content when compared to the same regions from healthy brain tissue.[56] In addition, it has been shown that mTOR inhibition can be neuroprotective against the toxic effects of amyloid-β plaques.[56] However, it is unclear if mTOR activity plays a role in driving the progression of the disease or if it is merely a consequence. There is also an increasing amount of evidence that indicates that the dysregulation of mTOR and autophagy are critical to the pathogenesis of Parkinson's Disease.[57]

Further, DEPTOR and mTOR dysregulation appear to play an important role in the progression of insulin resistance in type 2 diabetes. Skeletal muscle is particularly sensitive to insulin signalling and metabolic disorders, and is generally serves as one of the first indicators of insulin resistance.[58] It has also been shown that decreased DEPTOR levels in obese Zucker rats not only contributed to increased levels of basal protein synthesis, but that it favoured cap-dependent translation, despite reduced muscle mass when compared to their non-obese littermates.[59] In addition, this effect may contribute to overall resistance to the anabolic effects of exercise in muscle, which in turn can reduce the effectiveness of exercise as a means of treating type 2 diabetes.

Conclusions

Cellular anabolism and the control of translation is an extremely complex process, with new layers of complexity being uncovered routinely. The central nature of mTOR to these processes make it an enticing target to manipulate as a means to normalize cellular metabolism in a variety of conditions. This is especially true in light of mTOR's role in the downstream translational control of multiple types of transcripts. However, not only do the complexity of mTOR's many positive and negative feedback mechanisms can make achieving these ends difficult, but redundant mechanisms independent of mTOR can make indirect pharmacological control of these processes improbable, highlighting the need for specific targeting of the mTOR kinase, possibly through the manipulation of the intrinsic inhibitor DEPTOR. The recent development of second-generation mTOR kinase inhibitors such as Torin-1 is exciting, and has shown promising new possibilities for strategies designed to regulate this pathway. Other examples may include the tissue-specific delivery of advanced pharmacological inhibitors, mRNA of intrinsic inhibitors, or specific miRNA species, all of which may offer opportunities to mitigate the effects of many diseases in which dysregulation of these pathways is a common observation. Given that the prevalence of common dysregulation involving mTOR pathways in various anabolically aggressive diseases, a fundamental understanding of mTOR-centric regulation may offer interesting opportunities for potential common treatments. Understanding mTOR's downstream regulatory control over cap-dependent and cap-independent translational mechanisms may eventually yield an understanding of a deeply rooted regulation of cellular anabolism. A regulatory mechanism that does not simply turn anabolism on or off, but is able to integrate a complex signalling environment, prioritize classes of transcripts, and activate specific translational machinery to facilitate the production of proteins that are critical to normal cellular function.

Conflict of interest

Authors declear no confict of interst.

Submission statement

This manuscript is an original work that has not been previously published, nor will it be under consideration for publication by any other journal before a decision has been made by *Sports Medicine and Health Science*. If accepted, this manuscript will not be published elsewhere.

Authors' contributions

All contributing authors are represented in the list of authors appearing on the manuscript, and all authors approve of this manuscript and agree with submission for consideration of publication in Sports Medicine and Health Science.

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