THE ENZYMES

Structure, Function and Regulation of TOR complexes from Yeasts to Mammals
PART B

Edited by

Fuyuhiko Tamanoi

Michael N. Hall

VOLUME XXVIII

THE ENZYMES

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PART B

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The Enzymes

VOLUME XXVIII

STRUCTURE, FUNCTION AND REGULATION OF TOR COMPLEXES FROM YEASTS TO MAMMALS

PART B

Preface

This volume (Part B) is a continuation of Volume 27, "Structure, Function and Regulation of TOR Complexes from Yeasts to Mammals, Part A." The two volumes capture recent developments in the study of TOR signaling. They should be of interest to a wide range of researchers, including biochemists, developmental biologists, molecular biologists, and cancer researchers.

Volume 27 of "The Enzymes" focused on basic mechanisms of the TOR complexes and TOR signaling. In Volume 28, we extend the discussion to include topics such as chemotaxis, autophagy, and cell death. We also discuss the involvement of TOR signaling in energy homeostasis, aging, and cancer. Finally, a systems biology approach to TOR signaling is discussed. However, we realize that there are many more topics to be covered. These will be the focus of future volumes on TOR signaling.

We could not have put together this volume in a timely fashion without the efforts of a dedicated group of chapter authors. We are grateful to the authors. We thank Lisa Tickner and the production team at Elsevier for advice and encouragement. We also thank Gloria Lee of UCLA for assistance in communication, preparation, and editing of the chapters.

Fuyuhiko Tamanoi
Michael N. Hall
June 2010

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Contents

Preface xi

1. mTORC1-Mediated Control of Protein Translation

JAMIE M. DEMPSEY, SARAH J. MAHONEY, AND JOHN BLENIS

I. Abstract 1
II. Introduction 1
III. mTORC1 Targets and Control of Translation 5
IV. Conclusion 15
References 15

2. The TSC1–TSC2 Complex: A Key Signal-Integrating Node Upstream of TOR

CHRISTIAN C. DIBBLE AND BRENDAN D. MANNING

I. Abstract 21
II. Introduction 22
III. Downstream Functions: Regulation of the TOR Complexes by the TSC1–TSC2 Complex 26
IV. Upstream Regulation: The TSC1–TSC2 Complex Integrates Diverse Signals to Regulate mTORC1 30
V. Aberrant Inhibition of the TSC1–TSC2 Complex Leading to Activation of mTORC1 in the Majority of Human Tumors 38
VI. Important Outstanding Questions Concerning the TSC1–TSC2 Complex 40
References 41

3. AMPK Control of mTOR Signaling and Growth

DANA M. GWINN AND REUBEN J. SHAW

I. Abstract 49
II. AMPK is an Energy Sensing Kinase 50
III. mTOR is a Central Conserved Regulator of Growth and Metabolism 52
IV. AMPK Inhibits mTORC1 Through Phosphorylation of TSC2 and Raptor 54
V. AMPK and mTOR Have Opposing Roles in Specialized Metabolic Tissues in Mammals 57
VI. AMPK and TOR Function in Model Organisms to Control Growth, Metabolism, Autophagy, and Aging 60

VII. Therapeutic Implications 62
VIII. Future Perspectives 66
Acknowledgments 67
References 68

4. mTOR Signaling by Amino Acid Nutrients: Involvement of MAP4K3

LIJUN YAN AND RICHARD F. LAMB

I. Abstract 77
II. Nutrient Signaling to mTOR: Introduction 78
III. The Sensing of Amino Acid Nutrients 79
IV. Amino Acid Transporters and mTOR Signaling 82
V. Evidence That Intracellular Signaling Molecules Relay the Presence of Amino Acid Sufficiency to mTORC1 85
VI. MAP4K3 Participates in Amino Acid Signaling and Maintenance of Cell Size 87
VII. MAP4K3 Promotes Apoptosis via Regulation of the BH3-Only Proteins 90
Acknowledgments 92
References 92

5. mTORC2: The Other Facet of mTOR

CAROLINE TREINS AND JULIAN DOWNWARD

I. Abstract 99
II. Structure of mTOR Complex 2 (mTORC2) 100
III. Role of mTORC2 102
IV. Regulation of mTORC2 107
V. Potential of mTOR Inhibitors in Cancer Treatment 114
References 116

6. TORC2 and Chemotaxis in *Dictyostelium discoideum*

YOICHIRO KAMIMURA, HUAQING CAI, AND PETER N. DEVREOTES

I. Abstract 125
II. Introduction 126
III. The Life Cycle of *D. discoideum* 127
IV. The Components of TORC2–PDK–PKB Pathway in *D. discoideum* 128
V. The Signal Transduction Pathway for Chemotaxis 133
VI. Conclusion 139
Acknowledgments 140
References 140

7. The TOR-Mediated Regulation of Autophagy in the Yeast *Saccharomyces cerevisiae*

YOSHIAKI KAMADA AND YOSHINORI OHSUMI

I. Abstract 143
II. Autophagy and *ATG* Genes in Yeast 144
III. Induction of Autophagy by Nutrient Limitation 144
IV. Induction of Autophagy by TOR Inactivation 148
V. Regulation of Atg1 Kinase Complex by TOR Complex1 149
VI. Phosphorylation of Atg13 by TORC1 to Regulate Autophagy 155
VII. ULK Complex: Mammalian Counterpart of Yeast Atg1 Complex 157
VIII. Concluding Remarks 158
Acknowledgments 160
References 160

8. Conservation of the Tsc/Rheb/TORC1/S6K/S6 Signaling in Fission Yeast

AKIO NAKASHIMA AND FUYUHIKO TAMANOI

I. Abstract 167
II. Introduction 168
III. Overview of the TSC/Rheb/TORC1 Signaling in Fission Yeast 169
IV. PAS Assay and Detection of S6 in Fission Yeast 173
V. S6 Kinase in Fission Yeast 177
VI. Regulation of the TORC1 Signaling 178
VII. Effect of Rapamycin on the TORC1 Signaling 179
VIII. Future Prospects 182
Acknowledgments 182
References 182

9. The Systemic Control of Growth, Physiology, and Behavior by TOR Signaling in *Drosophila*

NATHALIE ARQUIER, RENALD DELANOUE, AND PIERRE LÉOPOLD

I. Abstract 189
II. Introduction 189
III. Growth Rate 191
IV. Developmental Timing 195
V. Feeding Behavior 197
VI. Fertility 198
VII. Control of Lifespan 200
References 201

10. Cell-Intrinsic Functions and Regulation of TOR Signaling in *Drosophila*

THOMAS P. NEUFELD

I. Abstract 205
II. Introduction 206
III. Genetic Screens: Identification of Network Components and Their Relationships 206
IV. Identification and Analysis of TOR-Dependent Cellular Functions in *Drosophila* 210
References 214

11. TOR Signaling and Cell Death

TAO WANG AND BRUCE A. EDGAR

I. Abstract 217
II. Introduction: Overview of the TOR Signaling Pathway 218
III. Anti-Cell Death Functions of TOR 220
IV. Cell Death Associated with the Upregulation of TOR 226
V. Autophagy Protects Cells from Neurodegenerative Diseases 231
VI. Conclusions and Prospectives 238
References 239

12. Elucidating TOR Signaling in *Chlamydomonas reinhardtii*

MARÍA ESTHER PÉREZ-PÉREZ AND JOSÉ L. CRESPO

I. Abstract 245
II. Introduction 246
III. Inhibition of TOR Signaling by Rapamycin in Chlamydomonas 247
IV. TOR Complexes 249
V. Control of Autophagy by TOR 254
VI. Perspectives 257
Acknowledgments 257
References 258

13. mTORC1 and mTORC2 in Energy Homeostasis

MARION CORNU AND MICHAEL N. HALL

I. Abstract 263
II. Introduction 263
III. mTORC1 in the Hypothalamus 264
IV. mTORC1 in Pancreatic β-Cells 267
V. mTORC1 and mTORC2 in Adipose Tissue 268
VI. mTORC1 and mTORC2 in Muscle 270
VII. mTORC1 in the Liver 271

VIII. Conclusion 273
Acknowledgments 273
References 273

14. TOR Signaling and Aging

MALENE HANSEN AND PANKAJ KAPAHI

I. Abstract 279
II. Introduction 280
III. TOR and Aging in *S. cerevisiae* 280
IV. TOR and Aging in *C. elegans* 285
V. TOR and Aging in *Drosophila* 289
VI. TOR and Aging in Mammals 291
VII. Conclusion and Future Perspectives 293
Acknowledgments 294
References 294

15. mTOR Signaling and Human Cancer

NAPHAT CHANTARAVISOOT AND FUYUHIKO TAMANOI

I. Abstract 301
II. Introduction 302
III. Frequent Activation of the mTOR Signaling in Human Cancer 303
IV. Identification of mTOR Mutations in Human Cancer 306
V. Inhibitors of the mTOR Signaling 309
VI. Future Prospects 313
Acknowledgment 314
References 314

16. Systems Biology and TOR: Past, Present, and Future

SOYEON I. LIPPMAN AND JAMES R. BROACH

I. Abstract 317
II. Introduction 318
III. Genome-Wide Approach to Defining the TOR Network 320
IV. Integration of Data 333
V. Computational Modeling and Prediction 336
VI. Future: TOR and Cancer 339
References 342

Author Index 349
Index 381

1

mTORC1-Mediated Control of Protein Translation

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I. Abstract

Eukaryotic cells expend vast amounts of resources during protein translation, and have therefore evolved mechanisms to police and regulate this process. At the center of this regulation lies the mTORC1 pathway. After sensing inputs from nutrients, growth factors, energy and cellular stresses, mTORC1 and its downstream effectors control overall protein synthesis from the generation of ribosomes to the direct regulation of translation initiation and elongation factors. This chapter reviews both recent and well-established examples of mTORC1 signaling and regulation of protein synthesis.

II. Introduction

Upon detecting changes in the extracellular environment, cells respond appropriately by altering gene expression. After transcription, an mRNA molecule is translated into a protein by ribosomes, and this protein

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synthesis can be broken down into three steps: translation initiation, elongation, and termination. In eukaryotes, translation initiation generally occurs by cap-dependent or internal ribosomal entry site (IRES)-dependent mechanisms. The majority of eukaryotic translation is initiated at the mRNA cap complex, which has led to a focus on the regulation and function of the proteins associated with the mRNA cap. A select group of eukaryotic messages can also be initiated when the 40S ribosomal subunit directly associates with an IRES sequence that is usually found within the 5′-untranslated region (UTR) (for reviews, see Ref. [1]). While IRES-mediated translation initiation is also regulated, this chapter will focus on the regulation of protein translation by the mTORC1 pathway via cap-dependent mechanisms.

Safeguarding cells from expending energy and resources on translation under conditions where there is no cellular need is achieved by precisely regulating protein synthesis and ribosomal biogenesis. The rate and timing of protein synthesis is carefully controlled in mammalian cells by signaling pathways that integrate and interpret extracellular cues. These cues affect multiple aspects of translation and the translational machinery, such as protein stabilization and localization, protein–protein interactions, and catalytic activity. Depending on the exact combination of signals, translational control occurs on a global, cap-dependent, or message-specific scale. Although many signaling pathways regulate protein synthesis, the mTORC1 pathway appears to be a master regulator, as it coordinates growth factor, amino acid, and energy inputs (see Chapters 3, 4, and 6 of Volume 27).

A. Translation: The Regulated Steps of Translation Initiation and Elongation

The platform and catalytic activity for translation is provided by ribosomes, which are composed of a large (60S) and a small (40S) subunit in eukaryotes. The building of each of the subunits, which consists of both rRNA and ribosomal proteins (RPs), is a complex process involving all three RNA polymerases and RP translation. The assembly of the 40S and 60S ribosomal subunits with the initiator tRNA, as well as certain eukaryotic translation initiation factors (eIFs) at the initiation codon of an mRNA transcript is referred to as translation initiation. Assembly of the translation initiation complex at the 5′-mRNA cap requires the recruitment of multiple proteins and preassembled protein complexes in a series of ordered events (Figure 1.1). The ternary complex consists of an initiator Met-tRNA$_i^{Met}$ bound to eIF2·GTP, which mediates the association of Met-tRNA$_i^{Met}$ with the 40S ribosomal subunit. The 43S preinitiation complex (PIC) is formed by binding of this charged 40S ribosomal subunit complex with the eIF3

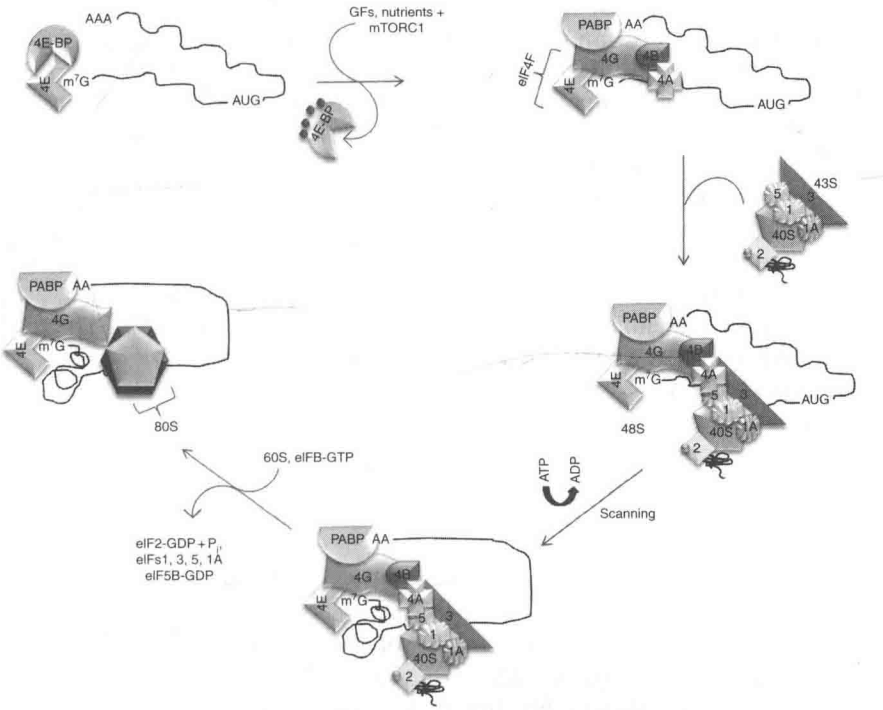

FIG. 1.1. Initiation of eukaryotic translation occurs after the activation of mTORC1 by growth factors and nutrients, resulting in the phosphorylation of 4E-BP1 and subsequent disassociation from eIF4E. The eIF4F protein complex binds to the mRNA creating docking sites for the 43S preinitiation complex (PIC), which is composed of the ternary complex, along with eIF1A, eIF1, eIF3, eIF5 bound to the 40S ribosomal subunit. After binding of the 43S PIC to the cap, the protein complex is termed the 48S PIC. Secondary structures in the 5′-untranslated region (UTR) are unwound in an ATP-dependent process by eIF4A as the 48S PIC scans to locate the AUG initiation codon. Once located, eIF2 hydrolyzes GTP, certain initiation factors are released and the 60S binds to the 40S subunit forming the translation-ready 80S ribosome.

complex (composed of five core subunits and seven to eight associated subunits), eIF1A, and eIF5 initiation factors. In this structure, the eIF3 complex also functions as a scaffold for signaling enzymes (reviewed in Refs. [2, 3]).

At the 5′ end of mRNAs with an m^7G (7-methylguanosine) cap, the cap binding protein (CBP) eIF4E is bound during steady-state translation, and is part of the eIF4F complex. The eIF4F complex also contains eIF4A and eIF4G. eIF4A is the RNA helicase responsible for unwinding secondary structures in the 5′-UTR, which is especially important for transcripts with highly structured 5′-UTRs. eIF4G serves as a scaffold for eIF4A, polyA

binding proteins (PABPs), and the eIF3 complex. PABPs bind to the polyA tail, helping to form an efficient translating machine by circularizing the mRNA–protein (mRNP) complex. The 48S PIC is formed after the 43S PIC binds to the eIF4F complex (Figure 1.1). Translation can be inhibited by the eIF4E-binding proteins (4E-BPs), which antagonize eIF4G's ability to bind to eIF4E and thus preventing assembly of the 48S PIC (reviewed in Refs. [2–6]).

Once the 48S PIC is formed at the mRNA cap complex, the 5′-UTR is scanned to locate the initiation codon (AUG). After the release of several initiation factors from the 40S ribosomal subunit, the 60S ribosomal subunit is able to bind, forming the functional 80S ribosome. Aided by eIF5, eIF2 hydrolyzes GTP and is subsequently released from the $tRNA_i^{Met}$. The eIF2 protein is recycled when eIF2B catalyzes the exchange of GDP for GTP on eIF2 (reviewed in Ref. [3]).

Translation elongation follows the initiation phase, and is supported by the eukaryotic elongation factors (eEF). After the 80S ribosome is assembled at the initiation codon, the initiation tRNA is in place so that the aminoacyl-tRNA that corresponds to the next codon can bind. The 60S ribosomal peptidyl transferase activity catalyzes peptide bond formation between the growing polypeptide and the aminoacyl-tRNA. Translocation of the ribosome relative to the tRNAs and mRNA complex is aided by the binding of eEF2·GTP to the ribosome. The activity of eEF2 can be suppressed allowing cells to control the elongation step of translation [7]. Phosphorylation by eEF2 kinase (eEF2K) results in this suppression, and multiple signaling pathways regulate the activity of eEF2K, including the mTORC1 pathway [8].

It is imperative that cells police protein translation, and each of the multitude of proteins involved in ribosome biogenesis, translation initiation, and elongation could hypothetically serve as points of regulation for cellular signaling pathways. Indeed, reversible protein phosphorylation regulates the function of most of the aforementioned translation proteins. For protein synthesis, the regulation of translation initiation serves as the rate-limiting step, but the mechanism detailing the order of factor addition has yet to be fully elucidated. Recent landmark experiments have identified protein kinases at the cap complex, which temporally control the initiation of translation (Figure 1.2).

The mechanisms for certain aspects of eukaryotic translation initiation, such as scanning and the order of initiation factor assembly at the cap, are not fully understood. It is known that many factors such as eIF4G, mTORC1, and eIF4B associate with the cap complex in a growth factor-sensitive manner [9] (Figure 1.2), which happens concurrently with the dissociation of translational repressors like 4E-BP1. How signaling events modulate initiation factor association and dissociation will likely be clarified in future studies helping to build on the model of translation initiation.

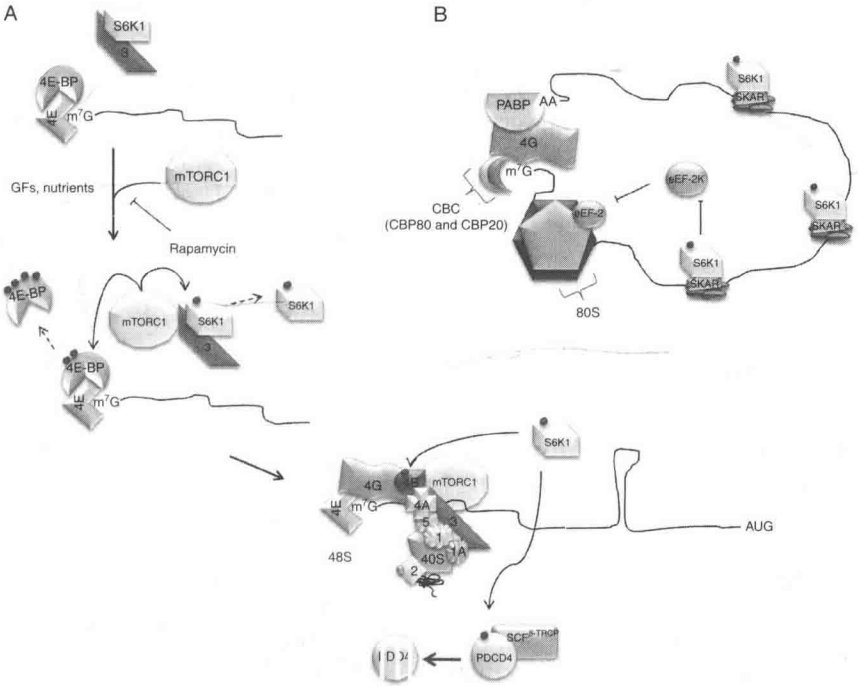

FIG. 1.2. mTORC1 and S6K1 associate with mRNA during translation. (A) The mTORC1 pathway is activated by growth factors and nutrients, resulting in the phosphorylation and assembly of initiation factors onto the mRNA cap complex. There is a pool of S6K1 associating with eIF3 that is not bound to the cap complex in unstimulated cells. S6K1 and eIF3 disassociate after growth factor stimulation. Concomitantly, 4E-BP1 and S6K1 are phosphorylated by an activated mTORC1. Many substrates involved in translation are then phosphorylated by S6K1, correlating with an increase in cap-dependent translation. These substrates include eIF4B and PDCD4. (B) During the pioneer round of translation, the scaffolding protein SKAR associates with the EJCs, and recruits an activated S6K1, correlating with an enhancement of the translation efficiency of these new mRNAs.

Although countless signaling events feed into regulation, this chapter will focus on mTORC1's contribution to regulation of translation initiation, elongation, and ribosome biogenesis.

III. mTORC1 Targets and Control of Translation

As discussed in great detail in Chapter 1 by Hall et al. in Volume 27, mTOR exists in two distinct protein complexes: mTORC1 and mTORC2 [10–15]. Briefly, mTORC1 contains mTOR, raptor (*r*egulatory-*a*ssociated

*p*rotein of m*TOR*), and mLST8 (also known as GβL) [16]. This complex directly phosphorylates 4E-BP1 and S6 kinase (S6K) to regulate ribosomal biogenesis, protein synthesis, and cell growth [17] in response to a variety of upstream growth factor, nutrient, and stress signals [18]. Raptor directly interacts with these substrates through the *TO*R *s*ignaling (TOS) motif, an essential phenylalanine followed by four alternating acidic and hydrophobic residues (FDIDL in S6K1 and FEMDI in 4E-BP1) [18–21].

A. mTORC1 Association with and Assembly of the Preinitiation Complex

The majority of the eIFs as well as many RPs [19–22] contain identified phosphorylation sites. Although the exact functions for many of these phosphorylation events are not fully understood, phosphorylation of many translation initiation factors positively or negatively regulates protein synthesis through interesting mechanisms. It is anticipated that protein kinases must be in close proximity to their appropriate targets in order for specific phosphorylation events to occur within the translation initiation complex. Recent work has demonstrated that the eIF3 complex acts as a conduit between mTORC1 activity, 4E-BP1 and S6K1 phosphorylation, and assembly of the translation initiation complex [9, 23] (Figure 1.2).

When the cell does not require enhanced protein synthesis (low energy, amino acids, and/or growth factors and hormones), an inactive S6K1 is bound to the eIF3 complex. Cap-binding assays and sucrose gradient analysis suggest that this complex is not bound to the cap complex, but is part of a free eIF3·S6K1 complex. After stimulation of the cells with insulin, mTORC1 interacts with eIF3, while S6K1 dissociates from the complex. Sucrose density gradients show mTORC1 associated with a larger mRNP complex [9], and this evidence as well as mTORC1 association with the mRNA cap pinpoints the mTORC1·eIF3 complex at the mRNA cap in stimulated cells (Figure 1.2). This interaction correlates with release of S6K1 from the eIF3 complex, as well as phosphorylation of S6K1 at its hydrophobic motif (Thr389). mTORC1 activity has also been reported to induce the stable recruitment of an eIF3 complex subunit, eIF3j [24]. In addition, eIF3j is reported to mediate the recruitment of the 40S subunit suggesting that mTORC1 binding may initiate the assembly of the 43S PIC[25]. mTORC1 also phosphorylates 4E-BP1 and its subsequent release from the cap complex also correlates with localization of mTORC1 at the cap. This event then initiates the assembly of the 48S PIC (see below).

B. mTORC1 Phosphorylation of 4E-BP1

The suppression of cap-dependent translation occurs when the hypophosphorylated form of the 16 kDa 4E-BP1 binds eIF4E and competitively inhibits the binding of eIF4G to eIF4E. After activation, mTORC1 phosphorylates 4E-BP1 releasing it from the cap complex so that eIF4E is free to interact with eIF4G, initiating translation (reviewed in Ref. [26]) (Figure 1.2). The phosphorylation of 4E-BP1 (Thr37, Thr46, Ser65, and Thr70) is proline-directed, and occurs in an ordered manner. The Thr37/Thr46 phosphorylation sites prime 4E-BP1 for subsequent phosphorylation at Ser65/Thr70. *In vitro* studies have shown mTORC1 *directly* phosphorylating the Thr37 and Thr46 sites, however, the phosphorylation of these sites is not always blocked by rapamycin, suggesting that rapamycin-insensitive kinases may contribute to these phosphorylation events *in vivo*. The phosphorylation of *Ser65/Thr70* is exclusively mTORC1-dependent in cells even though mTORC1 does not directly phosphorylate Ser65/Thr70 *in vitro*. An mTORC1-regulated kinase *or* phosphatase activity may control the phosphorylation status of these sites ([27] and reviewed in Ref. [28]). Inactivation of 4E-BP1 via mutations of the phosphosites to alanines or treatment with rapamycin reduces, but does not completely abolish, cap-dependent translation, indicating a low level of redundancy in translation signaling pathways (reviewed in Ref. [26]). The role of 4E-BP1 phosphorylation in promoting translation initiation may be message-specific, as overexpression of eIF4E results in increased translation of particular mRNAs with highly structured 5′-UTRs [29].

C. S6K and Targets Involved in the Regulation of Translation

The other well-known mTORC1 targets are the S6Ks, which belong to a family of basophilic serine/threonine kinases known as AGC kinases (reviewed by Jacinto in Chapter 7, Volume 27), which phosphorylate at basophilic motifs, particularly RXRXXS*/T* for S6K1. The most well-known S6K target is ribosomal protein S6 (rpS6), although the function of rpS6 phosphorylation remains unclear. Occasionally S6K will phosphorylate noncanonical basophilic motifs, such as that found in the substrate SKAR [30]. Other targets of S6K that are involved in the regulation of protein translation include eIF4B, PDCD4, and eEF2K.

1. rpS6

Upon activation by mTORC1, S6K1 is then able to phosphorylate many proteins at the cap complex to affect different kinds of activities (Figure 1.2). rpS6, which is a component of the 40S ribosomal subunit,

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