Amino acid signaling to mRNA translation: Central role of mTOR

S.R. Kimball, Department of Cellular & Molecular Physiology, The Pennsylvania State University College of Medicine, 500 University Drive, Hershey, PA 17033, USA. (Introduced by S. Bröer)

The increase in muscle protein synthesis that occurs in response to consumption of a complete meal by a fasted individual is a result not only of increased availability of the substrates used for synthesizing protein, *i.e.* amino acids, but also to nutrient- and hormone-induced activation of intracellular signaling pathways that regulate mRNA translation. Arguably, one of the most important nutrient-regulated signaling pathways in muscle involves a complex of proteins that includes the protein kinase referred to as the mammalian target of rapamycin (mTOR), the regulatory associated protein of mTOR (raptor), the Ras homolog enriched in brain (Rheb), the proline-rich Akt substrate (PRAS)40, LST8 (also known as GβL), and possibly other as yet unidentified proteins. Together, these proteins form the TOR complex 1 (TORC1). Nutrients such as the branched-chain amino acid leucine alter the conformation and/or composition of the TORC1 complex, resulting in increased mTOR protein kinase activity. For example, the amino acid-induced activation of TORC1 correlates with decreased amounts of raptor and PRAS40 present in mTOR immunoprecipitates, suggesting that amino acids alter the interaction of mTOR with both proteins. Amino acids also increase the proportion of Rheb present in the GTP bound form, an event that is critical for maximal TORC1 activation. However, the mechanism(s) through which amino acids act to alter either TORC1 conformation or Rheb association with GTP is incompletely defined. Upregulated nutrient signaling through TORC1 leads to increased phosphorylation of several proteins that play important roles in regulating the mRNA binding step in translation initiation including the eukaryotic initiation factor (eIF)4E binding protein (4E-BP)1 and the ribosomal protein S6 kinase S6K1. S6K1 subsequently phosphorylates eIF4B and eukaryotic elongation factor (eEF)2 kinase. Phosphorylation of 4E-BP1 by mTOR results in its release from the inactive 4E-BP1•eIF4E complex allowing the mRNA cap binding protein eIF4E to associate with eIF4G and eIF4A to form the active eIF4F complex. Phosphorylation of eIF4B, an activator of the RNA helicase activity of eIF4A, promotes its association with the eIF4F complex. Depending on the cell type, amino acid-induced assembly of the eIF4F complex can lead to increased global rates of protein synthesis and also to changes in the selection of mRNAs for translation, thereby altering the pattern of gene expression at the protein level. For example, activation of TORC1 preferentially increases the translation of mRNAs encoding proteins such as eEF1A, eEF2, and many ribosomal proteins, thereby increasing the capacity of the cell to synthesize protein. Our recent studies have identified a new target for TORC1 signaling, the catalytic ε-subunit of the guanine nucleotide exchange factor, eIF2B. In these studies, we found that leucine addition to leucine-deprived cells causes a redistribution of the eIF2Bε mRNA from an untranslated, non-polysomal fraction into polysomes, leading to increased incorporation of [^{35}S]methionine into eIF2Bε protein. The shift of eIF2Bε mRNA into polysomes and increased synthesis of eIF2Bε protein are both prevented by pre-treatment with the specific mTOR inhibitor rapamycin. Because eIF2B is an important regulator of global rates of protein synthesis, an increase in its expression is likely an important component in the increased capacity for mRNA translation associated with mTOR activation.

In summary, TORC1 represents a nexus through which nutrients and hormones act to acutely regulate mRNA translation. Moreover, by specifically increasing the translation of mRNAs encoding proteins involved in mRNA translation, activation of TORC1 upregulates the capacity to synthesize protein.

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