mTOR—What Does It Do?

M.N. Hall

ABSTRACT

Target of rapamycin (TOR) is a highly conserved serine/threonine kinase that controls cell growth and metabolism in response to nutrients, growth factors, cellular energy, and stress. TOR, which was originally discovered in yeast, is conserved in all eukaryotes including plants, worms, flies, and mammals. The discovery of TOR led to a fundamental change in how we think about cell growth. It is not a spontaneous process that just happens when building blocks (nutrients) are available, but rather a highly regulated, plastic process controlled by TOR-dependent signaling pathways.

TOR is found in 2 structurally and functionally distinct multiprotein complexes, TORC1 and TORC2. The 2 TOR complexes, like TOR itself, are highly conserved. Mammalian TORC1 (mTORC1) is rapamycin sensitive and contains mTOR, raptor, and mLST8. TORC1 in yeast and mammals mediates temporal control of cell growth by regulating several cellular processes, including translation, transcription, ribosome biogenesis, nutrient transport, and autophagy. mTORC2 is rapamycin insensitive and contains mTOR, rictor, mSIN1, PRR5, and mLST8. TORC2 in yeast and mammals mediates spatial control of cell growth by regulating the actin cytoskeleton. Thus, the 2 TOR complexes constitute an ancestral signaling network conserved throughout eukaryotic evolution to control the fundamental process of cell growth. As a central controller of cell growth, TOR plays a key role in development and aging and has been implicated in disorders such as cancer, cardiovascular disease, obesity, and diabetes. The challenge now is to understand the role of mTOR signaling to coordinate and integrate overall body growth in multicellular organisms.

TARGET OF RAPAMYCIN (TOR) is a highly conserved protein kinase and a central controller of cell growth and metabolism.[1–3] TOR was originally discovered in yeast but is conserved in all eukaryotes, including plants, worms, flies, and mammals. Mammalian TOR (mTOR) controls growth in response to nutrients (such as amino acids), growth factors (such as insulin, insulin-like growth factor [IGF]-1), and cellular energy (ATP). TOR activates cell growth by positively and negatively regulating several anabolic and catabolic processes, respectively, that collectively determine mass accumulation. In this context, it is important to note that cell growth refers to an increase in cell size rather than an increase in cell number that is a result of cell division. Whereas TOR is a central controller of cell growth, cyclin-dependent kinase is a central controller of cell division. Furthermore, the discovery of TOR led to a fundamental change in how we think about cell growth. It is not a spontaneous process that just happens when building blocks (nutrients) are available, but rather a highly regulated, plastic process controlled by TOR-dependent signaling pathways. The anabolic processes controlled by TOR include transcription, protein synthesis, ribosome biogenesis, nutrient transport, and mitochondrial metabolism. Conversely, TOR negatively regulates catabolic processes such as mRNA degradation, ubiquitin-dependent proteolysis, autophagy, and apoptosis.

TOR is found in 2 functionally and structurally distinct multiprotein complexes, TORC1 and TORC2 (mTORC1 and mTORC2 in mammals), each of which signals via a different set of effector pathways (Fig 1). mTORC1 is composed of raptor, mLST8, and mTOR and is rapamycin sensitive. mTORC2, consisting of rictor, mSIN1, PRR5, mLST8, and mTOR, is rapamycin insensitive. Raptor, a subunit of mTORC1, seems to be an adaptor that presents substrates to the mTOR catalytic subunit. The molecular roles of the other

From the Biozentrum, University of Basel, Switzerland.

Address reprint requests to Michael Hall, Biozentrum, University of Basel, Klingelbergstrasse 70, CH-4056 Basel, Switzerland. E-mail: M.Hall@unibas.ch

360 Park Avenue South, New York, NY 10010-1710

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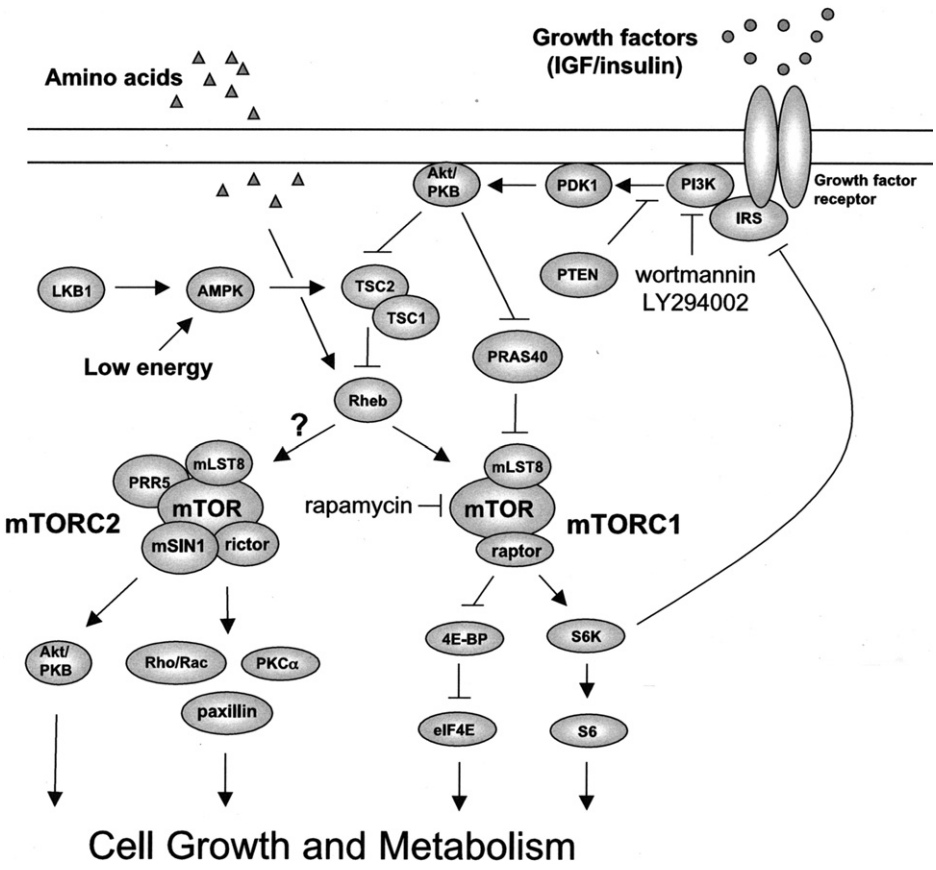

Fig 1. The mTOR signaling network.

subunits that constitute the 2 mTOR complexes are largely unknown. TOR itself is a large protein (around 280 kDa) with several domains. The amino-terminal half of TOR contains tandem HEAT (huntingtin, elongation factor 3, a subunit of protein phosphatase 2A and TOR1) repeats that are predicted to form an extended superhelical array with surfaces for protein–protein interactions. Indeed, most of the TORC subunits interact with the HEAT repeat region of TOR. The FRB domain, within a central region of TOR, is the binding domain for the FKBP12–rapamycin complex. FKBP12 is an intracellular proline isomerase that is "hijacked" by rapamycin to serve as a cofactor in the inhibition of TORC1. Point mutations in the FRB domain prevent binding of FKBP–rapamycin to TOR, thereby conferring rapamycin resistance. The FRB domain is presumably masked in TORC2 by a TORC2-specific subunit, which explains why TORC2 is rapamycin insensitive. The catalytic domain of TOR is near the carboxyl terminus. This kinase domain resembles a lipid (phosphatidylinositol) kinase domain, placing TOR in a group of atypical protein kinases referred to as the phosphatidylinositol kinase-related kinases (PIKK). TOR is the founding member of the PIKK family, which also contains ATM and DNA-PK among others. All members of the PIKK family, including TOR, are additionally characterized by so-called FAT and FATC domains. The FAT domain is between the HEAT repeats and the FRB domain. The FATC domain is at the extreme carboxyl terminus. FAT and FATC are always found together, which suggests that they interact. The best characterized phosphorylation substrates of mTOR are S6K and 4E-BP1, via which mTORC1 controls translation, and Akt/PKB, via which mTORC2 controls cell survival and likely other processes. Like TOR itself, the 2 TOR complexes and the overall architecture of the TOR signaling network seem to be conserved from yeast to human. Thus, the 2 TOR complexes constitute an ancestral signaling network conserved throughout eukaryotic evolution to control the fundamental process of cell growth.

The model organism *Saccharomyces cerevisiae,* also known as budding yeast, played an important role in elucidating TOR signaling. Rapamycin, a natural product secreted by soil bacteria as a weapon in microbiological warfare, evolved to inhibit microbes. Thus, yeast could be used to study the action of rapamycin, although at the time the studies were initiated, it was viewed as an outlandish approach to use yeast to study the mode of action of an immunosuppressive drug. The isolation of rapamycin-resistant yeast mutants led to the discovery of TOR, contributed to the elucidation of rapamycin action (FKBP–rapamycin complex formation) and defined the FKBP–rapamycin binding site in TOR. Subsequent studies in yeast also first described the 2 major branches of TOR signaling, each of which is mediated by a specific TOR complex. The study of rapamycin action in yeast illustrates the value of model organisms in biomedical