TOR signaling in mammals

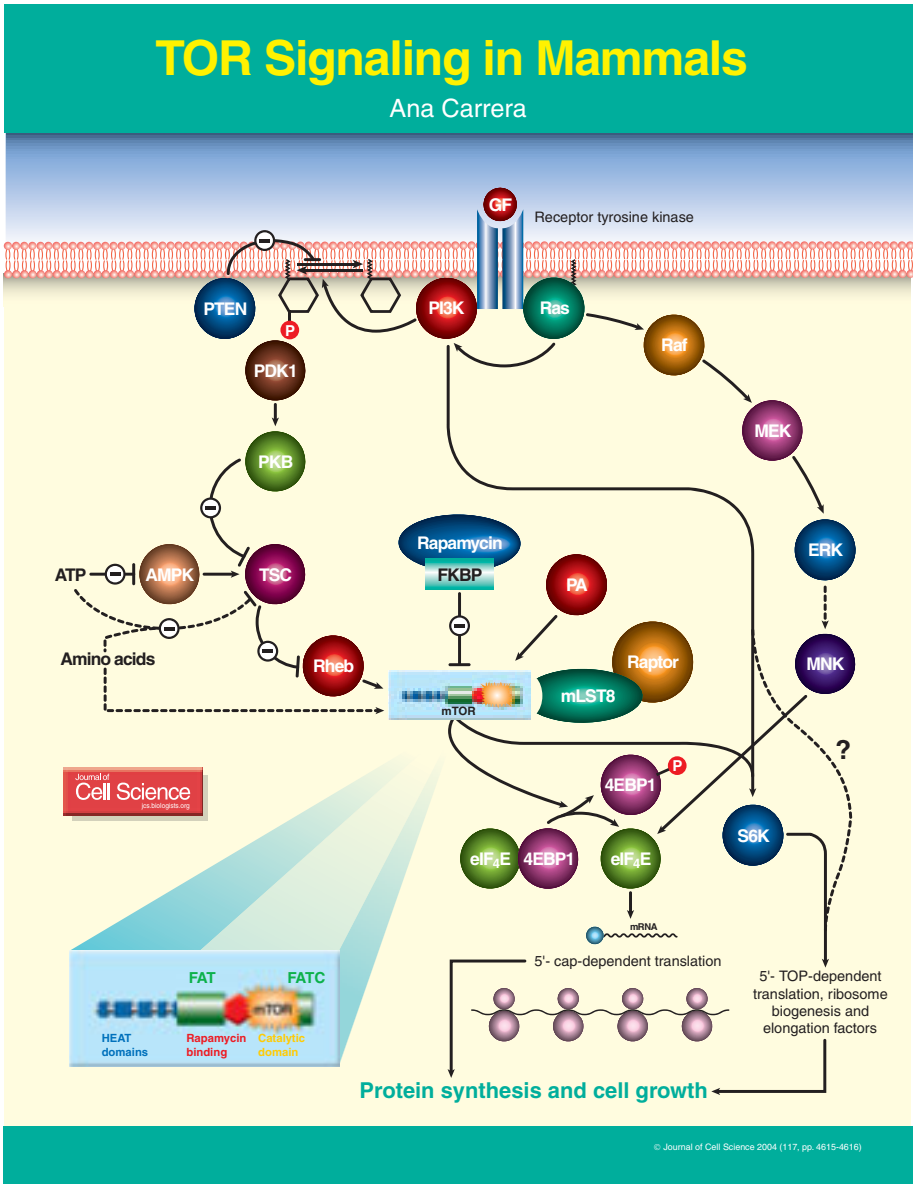
Ana C. Carrera

Department of Immunology and Oncology, Centro Nacional de Biotecnología/CSIC, Universidad Autónoma de Madrid, Cantoblanco, Madrid E-28049, Spain

(e.mail: acarrera@cnb.uam.es)

Journal of Cell Science 117, 4615-4616
Published by The Company of Biologists 2004
doi:10.1242/jcs.01311

Central to the pathways that induce cell growth in mammals is the murine target of rapamycin (mTOR), a multi-domain, 298 kDa, evolutionarily-conserved Ser/Thr kinase that is inhibited by the drug rapamycin (Schmelzle and Hall, 2000). mTOR exerts its effects by phosphorylating eukaryotic initiation factor 4E binding protein 1 (4EBP1), which inhibits 5′-cap-dependent mRNA translation (the majority of cellular translation) by binding and inactivating eIF4E. Phosphorylation of 4EBP1 releases eIF4E, allowing initiation of translation (Gingras et al., 2004). In addition to 4EBP1, mTOR also regulates translation via S6 kinase (S6K, formerly known as $p70^{s6K}$). This Ser/Thr kinase phosphorylates the ribosomal S6 protein, facilitating recruitment and translation of a specific mRNA subset that contains a 5′ polypyrimidine tract (5′-TOP) (Dufner and Thomas, 1999). 5′-TOP transcripts encode several ribosomal proteins and translation elongation factors. By acting on S6K, mTOR facilitates ribosome biogenesis and translation elongation (Gingras et al., 2004; Dufner and Thomas, 1999). To recognize 4EBP1 and S6K, mTOR must associate with a protein adaptor termed Raptor (for regulatory associated protein of mTOR). mTOR is found in a highly conserved complex that includes Raptor (Kim et al., 2002; Hara et al., 2002) and a protein of unknown function called mLST8 (Chen and Kaiser, 2003).



(See poster insert)

PI3K activation depends on several inputs, including nutrients (amino acids), energy (ATP) and growth factors (Schmelzle and Hall, 2000). Both ATP and amino acid deprivation result in mTOR inactivation, even in the presence of growth factors such as insulin (Schmelzle and Hall, 2000, Gingras et al., 2004; Dufner and Thomas, 1999). The mechanism by which amino acids and ATP activate mTOR is not completely clear. Nonetheless, under energy starvation conditions, the AMP-activated protein kinase (AMPK) phosphorylates and activates tuberous sclerosis protein 2 (TSC2, also termed tuberin) (Inoki et al., 2003), which inhibits mTOR in combination with TSC1 (hamartin) (Inoki et al., 2003; Potter et al., 2003; Gao et al., 2002). Amino acid deprivation has also been shown to regulate mTOR via the TSC complex (Gao et al., 2002). Restoration of ATP or amino acids induces mTOR activation, which is further increased by growth factor addition. Growth factors regulate mTOR via phosphoinositide 3-kinase (PI3K), protein kinase B (PKB/Akt) and TSC.

PI3K catalyzes generation of 3-polyphosphoinositides, whose levels are negatively controlled by the tumor suppressor PTEN (phosphatase and tensin homolog on chromosome 10). PI3K is a crucial mediator of cell growth. In fact, the transient kinetics of PI3K activation following growth factor receptor stimulation determine the transient induction of growth signaling pathways such as S6K (Alvarez et al., 2003). The PI3K p85 regulatory subunit associates with mTOR, and this

complex is required for mTOR-mediated S6K activation (Gonzalez-Garcia et al., 2002). PI3K also mediates S6K activation via its effector, PDK1 (3-phosphoinositide-dependent protein kinase) (Romanelli et al., 2002), and regulates 5′-TOP mRNA translation independently of S6K (Stolovich et al., 2002). In addition, active PI3K neutralizes the action of the TSC complex (Inoki et al., 2003; Potter et al., 2003; Gao et al., 2002). It was recently reported that the small GTPase Rheb (Ras homologue enriched in brain) is required for mTOR activation. Rheb acts as a bridge between TOR and TSC, because it is regulated directly by the TSC2 GAP activity (Manning and Cantley, 2003). To release mTOR from TSC inhibitory action, growth factors such as insulin or serum activate PI3K and its effector, PKB, which in turn phosphorylates and inactivates TSC2 (Inoki et al., 2002). Nutrients and energy levels also regulate TSC complex activity (see above). Further studies are needed to clarify the crosstalk required to bring together ATP, nutrient and mitogen signals for mTOR activation.

References

Alvarez, B., Garrido, E., Garcia-Sanz, J. A. and Carrera, A. C. (2003). Phosphoinositide 3-kinase activation regulates cell division time by coordinated control of cell mass and cell cycle progression rate. *J. Biol. Chem.* **278**, 26466-26473.

Chen, E. J. and Kaiser, C. A. (2003). LST8 negatively regulates amino acid biosynthesis as a component of the TOR pathway. *J. Cell Biol*. **161**, 333-347.

Dufner, A. and Thomas, G. (1999) Ribosomal S6 kinase signaling and the control of translation. *Exp Cell Res.* **253**, 100-109.

Gao, X., Zhang, Y., Arrazola, P., Hino, O., Kobayashi, T., Yeung, R. S., Ru, B. and Pan, D. (2002). Tsc tumour suppressor proteins antagonize amino-acid-TOR signalling. *Nat. Cell Biol*. **4**, 699-704.

Gingras, A. C., Raught, B. and Sonenberg, N. (2004). mTOR signaling to translation. *Curr. Top. Microbiol. Immunol*. **279**, 169-197.

Gonzalez-Garcia, A., Garrido, E., Hernandez, C., Alvarez, B., Jimenez, C., Cantrell, D. A., Pullen, N. and Carrera, A. C. (2002). A new role for the p85-phosphatidylinositol 3-kinase regulatory subunit linking FRAP to p70 S6 kinase activation. *J. Biol. Chem*. **277**, 1500-1508.

Hara, K., Maruki, Y., Long, X., Yoshino, K., Oshiro, N., Hidayat, S., Tokunaga, C., Avruch, J. and Yonezawa, K. (2002). Raptor, a binding partner of target of rapamycin (TOR), mediates TOR action. *Cell* **110**, 177-189.

Inoki, K., Li, Y., Zhu, T., Wu, J., Guan, K. L. (2002) TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling. *Nat. Cell Biol.* **4**, 648-657.

Inoki, K., Zhu, T. and Guan, K. L. (2003). TSC2 mediates cellular energy response to control cell growth and survival. *Cell* **115**, 577-590.

Kim, D. H., Sarbassov, D. D., Ali, S. M., King, J. E., Latek, R. R., Erdjument-Bromage, H., Tempst, P. and Sabatini, D. M. (2002). mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery. *Cell* **110**, 163-175.

Manning, B. D. and Cantley, L. C. (2003). Rheb fills a GAP between TSC and TOR. *Trends Biochem. Sci.* **28**, 573-576.

Potter, C. J., Pedraza, L. G., Huang, H. and Xu, T. (2003). The tuberous sclerosis complex (TSC) pathway and mechanism of size control. *Biochem. Soc. Trans.* **31**, 584-586.

Romanelli, A., Dreisbach, V. C. and Blenis, J. (2002). Characterization of phosphatidylinositol 3-kinase-dependent phosphorylation of the hydrophobic motif site Thr(389) in p70 S6 kinase 1. *J. Biol. Chem*. **277**, 40281-40289.

Schmelzle, T. and Hall, M. N. (2000). TOR, a central controller of cell growth. *Cell* **103**, 253-262.

Stolovich, M., Tang, H., Hornstein, E., Levy, G., Cohen, R., Bae, S. S., Birnbaum, M. J. and Meyuhas, O. (2002). Transduction of growth or mitogenic signals into translational activation of TOP mRNAs is fully reliant on the phosphatidylinositol 3-kinase-mediated pathway but requires neither S6K1 nor rpS6 phosphorylation. *Mol. Cell. Biol*. **22**, 8101-8113.

Cell Science at a Glance on the Web
Electronic copies of the poster insert are available in the online version of this article at jcs.biologists.org. The JPEG images can be downloaded for printing or used as slides.