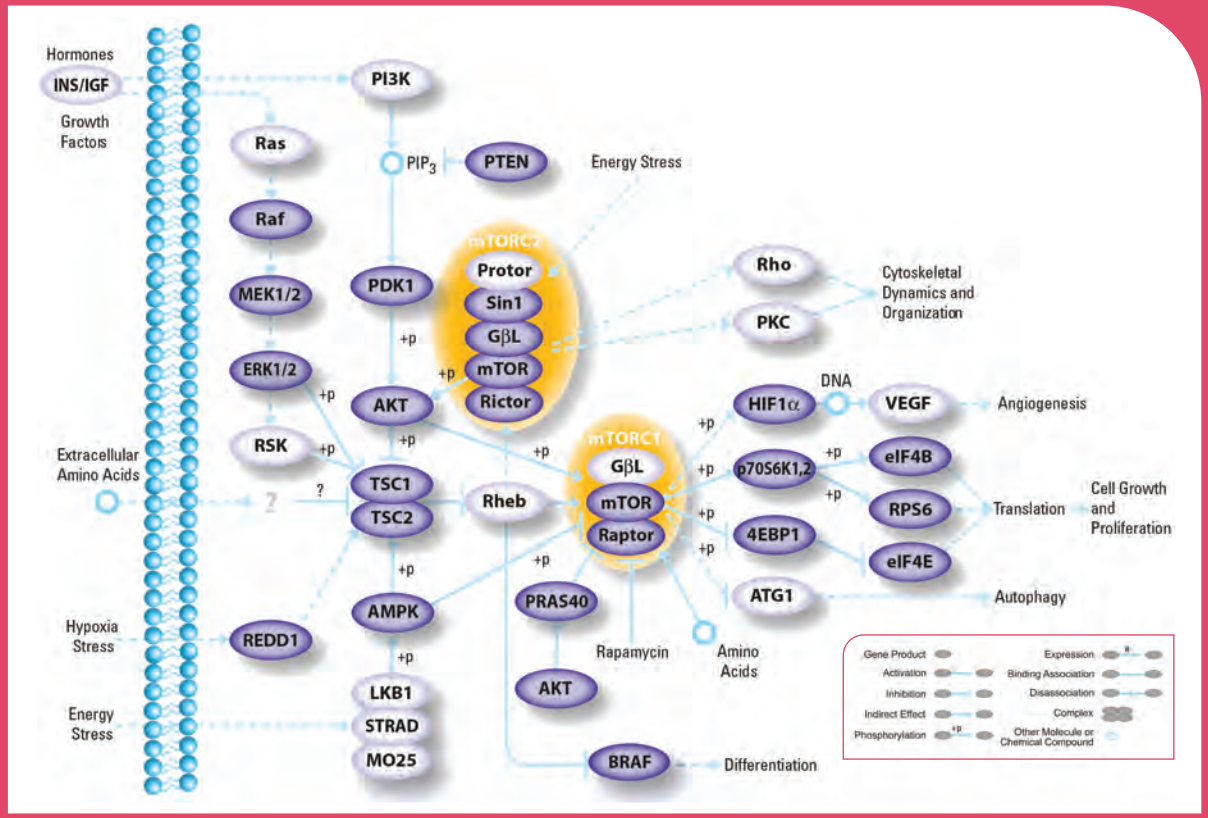
mTOR

The mammalian target of rapamycin (mTOR) is a member of the ATM-related family of kinases. Studies of mTOR demonstrate a central role in integrating signals that relay information pertaining to the conditions of the cellular environment. Via the mTOR pathway, levels of energy stress, hypoxia stress, and the availability of nutrients, growth factors, and hormones are sensed so that translation initiation, ribosome biogenesis, and transcription can be appropriately regulated (*reviewed in*[1]). Ultimately, mTOR signaling leads to responses in cytoskeletal dynamics and organization, cellular growth and proliferation, apoptosis, and autophagy. The original TOR homolog was identified in yeast as the direct target of the cell cycle arresting activity of the immunosuppressive drug, rapamycin[2]. Through its interaction with FKBP12, rapamycin exerts its effects by binding the mTOR Complex 1 (mTORC1) and inhibiting mTOR activity. In addition to mTORC1, a second mTOR complex, mTORC2, has been identified. This complex was originally identified as a rapamycin-insensitive complex [3,4]; however more recent reports suggest that in certain cases, mTORC2 also can display sensitivity to rapamycin (*reviewed in*[5]). The mTORC1 and mTORC2 are defined by the association of the mTOR kinase with either raptor (mTORC1) or rictor (mTORC2). In addition to their structural differences, the two complexes differ functionally. mTORC1 signaling mainly influences the initiation of protein translation and cell size, while mTORC2 signaling mainly has effects on cytoskeletal dynamics and organization (*reviewed in*[1]). The discovery that both mTORC1 and mTORC2 exhibit sensitivity to rapamycin has resulted in new implications for rapamycin based therapeutic strategies. More studies of mTOR signaling mechanisms will be required for the consideration of these differential responses in the development of approaches for therapeutic targeting of mTOR signaling.

References

1. K. Inoki, H. Ouyang, Y. Li, K. L. Guan, Microbiol. Mol Biol Rev. 69, 79-100 (2005).
2. J. Heitman, N. R. Movva, M. N. Hall, Science 253, 905-909 (1991).
3. D. D. Sarbassov et al., Curr. Biol. 14, 1296-1302 (2004).
4. E. Jacinto et al., Nat Cell Biol. 6, 1122-1128 (2004).
5. D. A. Foster and A. Toschi, Cell Cycle. 8, 1026-1029 (2009).



In response to environmental conditions, the mammalian target of rapamycin (mTOR) integrates a number of cellular signals for the regulation of a variety of basic cellular processes. Dysregulation of the mTOR pathway has been observed in a range of human malignancies; thus, the mTOR kinase is considered to be a promising target for cancer therapies.

The mTORC1 and mTORC2 complexes receive information on the environmental status via MAPK, AKT, and AMPK signaling. mTORC1 complexes composed of mTOR, raptor,and GbetaL, integrate these signals by phosphorylating substrates involved in protein translation such as p70S6K, 4EBP1, and 4EBP2. The signals which activate mTORC2 signaling are less understood. The mTORC2 complex, composed of mTOR, Rictor, GbetaL, sin1, and protor, functions as the kinase which phosphorylates AKT, and activates PKC and Rho for the modulation of Cytoskeletal activities. The complex formed by TSC1 and TSC2, which is inhibited by MAPK and AKT signaling, is a major negative regulator of mTOR signaling. (Figure adapted from the KEGG Pathway Database www.genome.jp/kegg/pathway/hsa/hsa04150.html)

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