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SIN1/MIP1 Maintains rictor-mTOR Complex Integrity and Regulates Akt Phosphorylation and Substrate Specificity

Estela Jacinto, 1, 3, 4 Valeria Facchinetti, 1, 4, 5 Dou Liu, 1 Nelyn Soto, 1 Shinui Wei, 1 Sung Yun Jung, 1 Qiaoliang Huang, 1 Jun Qin, 1, 3, 4 and Bing Su 1, 4

1 Department of Immunology, University of Texas M. D. Anderson Cancer Center, Houston, TX 77030, USA
2 Department of Physiology and Biophysics, UMDNJ-Robert Wood Johnson Medical School, Piscataway, NJ 08854, USA
3 Verna and Jonas M. McLaren Department of Biochemistry and Molecular Biology, and Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX 77030, USA
4 These authors contributed equally to this work.
5 Contact: bsu@mdanderson.org (B.S.); jqs1@bcm.tmc.edu (J.Q.)
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SUMMARY

Mammalian target of rapamycin (mTOR) controls cell growth and proliferation via the raptor-mTOR (TORC1) and rictor-mTOR (TORC2) protein complexes. Recent biochemical studies suggested that TORC2 is the elusive PKD2 for Akt/PKB Ser473 phosphorylation in the hydrophobic motif. Phosphorylation at Ser473, along with Thr308 of its activation loop, is deemed necessary for Akt function, although the regulatory mechanisms and physiological importance of each phosphorylation site remain to be fully understood. Here, we report that SIN1/MIP1 is an essential TORC2/PKD2 subunit. Genetic ablation of sin1 abolished Akt-Ser473 phosphorylation and disrupted rictor-mTOR interaction but maintained Thr308 phosphorylation. Surprisingly, defective Ser473 phosphorylation affected only a subset of Akt targets in vivo, including FoxO1/3a, while other Akt targets, TSC2 and GSK3, and the TORC1 effectors, S6K and 4E-BP1, were unaffected. Our findings reveal that the SIN1-rictor-mTOR function in Akt-Ser473 phosphorylation is required for TORC2 function in cell survival but is dispensable for TORC1 function.

INTRODUCTION

Cell growth and proliferation are orchestrated by signaling networks in response to environmental cues such as nutrients, growth factors, and hormones. An important player in the control of cell growth is the evolutionarily conserved protein kinase, target of rapamycin (TOR) (Jacinto and Hall, 2002; Sarbassov et al., 2004; Wulschleger et al., 2006). In addition to being a central regulator of cell growth (size/mass increase), proliferation, apoptosis, and metabolism, mammalian TOR (mTOR) is also linked to the PI3K/PTEN/Akt/TORC signaling pathway, where genetic mutations of many components in this pathway result in the development of a wide variety of cancers. Thus the mTOR pathway is an attractive anticancer drug target (Guertin and Sabatini, 2005; Hay, 2005).

Recent studies have revealed that mTOR, similar to its yeast counterpart, resides in two protein complexes (Inoki and Guan, 2006; Wulschleger et al., 2006). Mammalian TOR complex 1 (TORC1) is rapamycin-sensitive and consists of mTOR, raptor, and mLst8 (Gly), which are the orthologs of yeast TOR1/2, KOG1, and LST8, respectively (Hara et al., 2002; Kim et al., 2002; 2003; Loweth et al., 2002). TORC1 is activated by nutrients, growth factors/hormones, and energy signals and is inhibited by rapamycin. Activation of TORC1 results in phosphorylation of the translational regulators S6K and 4E-BP, which augments protein synthesis (Gingras et al., 2004). Both raptor and mLst8 positively regulate TORC1 functions, but the detailed mechanism of this regulation is unclear. Mammalian TORC2 is rapamycin insensitive and contains mTOR, rictor (mAVOS), and mLST8 (Jacinto et al., 2004; Sarbassov et al., 2004). Yeast TOR2 contains TOR2, AVOS, LST8, and additionally AVO1, AVO2, and BRT51 (Loweth et al., 2002; Reineke et al., 2004; Wedaman et al., 2003). Whether a distantly related gene msr1? (Human Stress Activated Protein Kinase Interacting Protein 1) is a functional equivalent of AVO1 needs further examination (Loweth et al., 2002; Reineke et al., 2004; Wulschleger et al., 2006). The function of mammalian TORC2 is less defined than that of TORC1 but is believed to be involved in actin cytoskeleton reorganization (Jacinto et al., 2004; 2005; Loweth et al., 2002; Sarbassov et al., 2004). Recent biochemical studies showed that TORC2 was able to phosphorylate the growth factor-regulated kinase Akt/PKB (Hersko and Mueckler, 2005; Sarbassov et al., 2005b). Akt/PKB is a member of the AGC kinase family, which also includes S6K, RSK, SGK, and PPK (Peterson and Schreiber, 1999; Woodgett, 2005). Most members of this
Dr. Jacinto Studying Field Zoology
University of the Philippines
Dr. Jacinto at Lab Outing
University of Basel, Switzerland
Lab Outing with Dr. Jacinto’s Team at UMDNJ
I AM NEW JERSEY
Love for science turns to urgent need when her daughter gets sick

ESTELA JACINTO
A passion to know

When Estela Jacinto, an associate professor at Robert Wood Johnson Medical School, became a new student on the horizon of her career, she tells about the difficulties she faced and how her love for science turned into an urgent need.