Doctoral thesis/dissertation Digest Form

Thesis/dissertation Title

Genetic analysis of the subunit architecture that determines the plasma membrane localization of TOR complex 2

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The Target of Rapamycin (TOR) is an evolutionarily conserved serine/threonine kinase that controls the cellular metabolism, growth, and proliferation in response to environmental cues, such as nutrient availability, stress, and growth factors. Biochemical analysis revealed that the TOR kinase assembles into two distinct protein complexes named TOR complex 1(TORC1) and TOR complex 2 (TORC2). TORC2 is known to phosphorylate Akt, a well characterized effector of phosphatidylinositol 3-kinase (PI3K) that plays important roles in the pathogenesis of human cancers. However, the activation mechanism of TORC2 in response to PI3K has remained elusive.

The objective of this study is to unveil the mechanisms that govern TORC2 regulation by dissecting the roles of each TORC2 regulatory subunits in fission yeast. Given that the CRIM domain of the Sin1 subunit is found to mediate the substrate recognition and recruitment for the complex, other conserved domains on the regulatory subunits might also hold important functions for TORC2 regulation. Furthermore, the molecular functions of Bit61/Bit2 have been a mystery since its discovery over a decade ago and these subunits are often ignored in the study of TORC2.

In this study, the important function of Bit61/Bit2 in TORC2 regulation is described. The subunit organization of TORC2 is delineated through characterization of the interactions among Bit61/Bit2, Ste20, and Sin1. The data collected in this study suggest that Bit61/Bit2 and the Sin1-PH domain have a redundant role in the plasma membrane localization of TORC2, which is essential for the control of cellular metabolism and proliferation.