

特別セミナー

Upstream regulators of mTOR for cellular nutrient/energy sensing

講師：Sung Ho Ryu先生

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Upstream regulators of mTOR for cellular nutrient/energy sensing

Sung Ho Ryu

Division of Molecular & Life Sciences, Pohang University of Science and
Technology

Pohang, 790-784, Korea

The mammalian target of rapamycin with raptor forms the protein complex (mTORC1) that plays a central role in the regulation of cell growth in response to environmental cues such as mitogen, amino acid, and glucose. The mechanism of mTORC1 signaling in molecular detail has been an important question for understanding how cell maintain energy homeostasis as well as for finding drug targets for the pathological situations as cancer and diabetes. Here, we propose two novel molecular networks upstream of mTORC1 to sense the availabilities of these essential nutrients in mammalian cells. We found that phospholipase D2 (PLD2) together with small GTPase Rheb, two known activators of mTORC1, forms a positive feed-forward loop to sense mitogen and amino acid level and thereby to activate mTOR kinase activity. Phosphatidic acid (PA), an enzymatic product of PLD2, modulates the affinity of GTP-bound Rheb onto mTOR kinase domain, resulting in full activation of mTOR kinase activity. We also identified that the glycolytic enzyme glyceraldehydes-3-phosphate dehydrogenase (GAPDH) binds Rheb and inhibits mTORC1 signaling. Under low glucose conditions, GAPDH sequesters Rheb from binding to mTORC1 and thereby inhibits mTORC1 signaling. We found that glyceraldehydes-3-phosphate (Gly-3-P), a glycolytic intermediate that binds GAPDH, destabilizes the Rheb-GAPDH interaction, and thereby activates mTORC1 signaling, which explains the molecular mechanism how glucose availability is sensed by mTORC1. Therefore, we suggest GAPDH-Rheb interaction as a network module that can regulate mTORC1 in response to glucose availability independently of AMPK-tuberous sclerosis complex pathway which has been known as sensing machinery for glucose-dependent ATP level. Taken together, mTORC1 is challenged by various signals and this is the basis of cellular homeostasis. To sense various signals, mTORC1 interacts dynamically with diverse sets of molecular complexes such as PLD2/PA/Rheb and Gly-3-P/GAPDH/Rheb for mitogen/amino acids and glucose sensing, respectively. Our results show that these types of dynamic molecular interactions play an important role for mTORC1 to make a smart decision in response to various upstream signals, generating potential molecular targets for mTORC1-related diseases.

Sung Ho Ryu先生は、脂質性シグナル伝達に関する研究で世界一流の成果を発表されており、最近では、mTORシグナル経路についての研究も精力的に行われています。本セミナーでは、様々なシグナル伝達系がどのように脂質性シグナル系とクロストークしているかについて、最近の知見をまじえてお話しして頂きます。皆さん奮ってご参加ください。

問い合わせ先：生命システム医学専攻 金保安則 ykanaho@md.tsukuba.ac.jp (内3282)