Investigation on Molecular Link Between the Phosphatidylinositol 3-Kinase Signaling Pathway and the Cell Cycle Machinery

2000 Fiscal Year Final Research Report Summary

Investigation on Molecular Link Between the Phosphatidylinositol 3-Kinase Signaling Pathway and the Cell Cycle Machinery

Research Project

Project/Area Number

11670035

Research Category

Grant-in-Aid for Scientific Research (C)

Allocation Type

Single-year Grants

Section

一般

Research Field

General physiology

Research Institution

Kanazawa University

Principal Investigator

TAKUWA Noriko Kanazawa University School of Medicine, Research Associate, 医学部, 助手 (70150290)

Project Period (FY)

1999 – 2000

Keywords

Phosphtidylinositol 3-kinase / cyclin D / cell cycle / p70^<s6k> / mTOR / NIH3T3 fibroblasts

Research Abstract

Phosphatidylinositol (PI) 3-kinase is required for G1 to S phase cell cycle progression stimulated by a variety of growth factors, and is implicated as a regulator for activation of several downstream targets, including p70^<S6K>. However, molecular mechanisms by which PI 3-kinase is engaged in the activation of the cell cycle machinery is not fully understood. Here we report that a transient expression of wild type p110α catalytic subunit of PI 3-kinase was capable of inducing cyclin D1 protein in quiescent NIH3T3 (M17) fibroblasts. This effect of p110 was strongly attenuated by either the PI 3-kinase inhibitor LY294002 or rapamycin, but not by an induced expression of a dominant negative (DN-) Ras, Ras(Asn17). The expression of wild type p110 also greatly potentiated epidermal growth factor (EGF)-stimulated cyclin D1 protein expression. Conversely, the expression of a DN-form of either p110 or p85

regulatory subunit of PI 3-kinase strongly inhibited EGF-induced up-regulation of cyclin D1 protein. LY294002 and another PI 3-kinase inhibitor wortmannin completely abrogated EGF-stimulated increases in both mRNA and protein levels of cyclin D1, pRb phosphorylation and S phase entry. However, rapamycin had little inhibitory effect, if any, on either of these events despite potent p70^<S6K> inhibition throughout the G1 phase. These results indicate that PI 3-kinase is both necessary and sufficient for up-regulation of cyclin D1, with the downstream mTOR -p70^<S6K> signaling pathway differentially required depending on cellular conditions.

Research Products (12 results)

All | Other

All | Publications (12 results)

[Publications] H.Okamoto, et al.: "Inhibitory regulation of Racactivation, membrane ruffling and cell migration by sphingosine-1-phosphate receptor EDG5 ; but not EDG1orEDG3."Mol.Cell.Biol.. 20(24). 9247-9261 (2000)

[Publications] H.Mitsui, et al.: "The MEK1-ERK-MAP Kinase Pathway and the PI 3-Kinase-Akt pathway independently mediate anti-apoptotic signals in HepGZ liver cancer cells."Int.J.Cancer. (in press). (2001)

[Publications] N.Takuwa, et al.: "Regulation of cell cycle molecules by the Ras effector system."Mol.Cell.Endocrinol.. (in press). (2001)

[Publications] Y.Takuwa, et al.: "Subtype-specific,differential activities of the EDG family receptors for sphingosine-1-phosphate, a novel lysophospholipid mediator"Mol.Cell.Endocrinol.. (in press). (2001)

[Publications] N.Takuwa, Y.Fukui and Y.Takuwa.: "Cyclin D1 Expression Mediated by Phosphatidylinositol 3-Kinase through mTOR-p70S6K-Independent Signaling in Growth Factor-Stimulated NIH 3T3 Fibroblasts."Mol.Cell.Biol.. 19(2). 1346-1358 (1999)

[Publications] K.Gonda, H.Okamoto, N.Takuwa, Y.Yatomi, H.Okazaki, T.Sakurai, S.Kimura, R.Sillard, K.Harii and Y.Takuwa.: "The novel sphingosine 1-phosphate receptor AGR16 is coupled via pertussis toxin-sensitive and insensitive G-proteins to multiple signalling pathways."Biochem.J.. 337. 67-75 (1999)

[Publications] H.Okamoto, N.Takuwa, Y.Yatomi, K.Gonda, H.Shigematsu and Y.Takuwa.: "EDG3 is a functional receptor specific for sphingosine-1-phosphate and sphingosylphosphorylcholine with signaling characteristics distinct from EDG1 and AGR16."Biochem.Biophys.Res.Commun.. 260(1). 203-208 (1999)

[Publications] H.Okamoto, N.Takuwa, T.Yokomizo, N.Sugimoto, S.Sakurada, H.Shigematsu and Y.Takuwa.: "Inhibitory Regulation of Rac Activation, Membrane Ruffling and Cell Migration by Sphingosine-1-Phosphate Receptor EDG5, but not EDG1 or EDG3."Mol.Cell.Biol.. 20(24). 9247-9261 (2000)

[Publications] N.Takuwa and Y.Takuwa.: "Regulation of cell cycle molecules by the Ras effector system."Mol.Cell.Endocrinol.. (in press). (2001)

[Publications] Y.Takuwa, H.Okamoto, N.Takuwa, K.Gonda, N.Sugimoto and S.Sakurada.: "Subtype-Specific, Differential Activities of the EDG Family Receptors for Sphingosine-1-Phosphate, a Novel Lysophospholipid Mediateor."Mol.Cell.Endocrinol.. (in press). (2001)

[Publications] H.Mitsui, N.Takuwa, T.Maruyama, H.Maekawa, M.Hirayama, T.Saratari, N.Hashimoto, Y.Takuwa and S.Kimura.: "The MEK1-ERK-MAP kinase pathway and the PI3-kinase-Akt pathway independently mediate anti-apoptotic signals in HEPG2 liver cancer cells."Int.J.Cancer.. (in press). (2001)

[Publications] H.Mitsui, N.Takuwa, T.Maruyama, H.Maekawa, M.Hirayama, T.Saratari, N.Hashimoto, Y.Takuwa and S.Kimura.: "The MEK1-ERK-MAP kinase pathway and the PI3-kinase-Akt pathway independently mediate anti-apoptotic signals in HEPG2 liver cancer cells."Am.J.Physiol.. 278. C57-C65 (2000)