References

Aguirre, V., Werner, E. D., Giraud, J., Lee, Y. H., Shoelson, S. E., and White, M. F. (2002). Phosphorylation of Ser307 in insulin receptor substrate-1 blocks interactions with the insulin receptor and inhibits insulin action. J Biol Chem *277*, 1531-1537.

Akimoto, K., Takahashi, R., Moriya, S., Nishioka, N., Takayanagi, J., Kimura, K., Fukui, Y., Osada, S., Mizuno, K., Hirai, S., *et al.* (1996). EGF or PDGF receptors activate atypical PKClambda through phosphatidylinositol 3-kinase. Embo J *15*, 788-798.

Alessi, D. R., Andjelkovic, M., Caudwell, B., Cron, P., Morrice, N., Cohen, P., and Hemmings, B. A. (1996). Mechanism of activation of protein kinase B by insulin and IGF-1. Embo J *15*, 6541-6551.

Alessi, D. R., James, S. R., Downes, C. P., Holmes, A. B., Gaffney, P. R., Reese, C. B., and Cohen, P. (1997). Characterization of a 3-phosphoinositide-dependent protein kinase which phosphorylates and activates protein kinase Balpha. Curr Biol *7*, 261-269.

Antonetti, D. A., Algenstaedt, P., and Kahn, C. R. (1996). Insulin receptor substrate 1 binds two novel splice variants of the regulatory subunit of phosphatidylinositol 3-kinase in muscle and brain. Mol Cell Biol *16*, 2195-2203.

Arcaro, A., Volinia, S., Zvelebil, M. J., Stein, R., Watton, S. J., Layton, M. J., Gout, I., Ahmadi, K., Downward, J., and Waterfield, M. D. (1998). Human phosphoinositide 3-kinase C2beta, the role of calcium and the C2 domain in enzyme activity. J Biol Chem *273*, 33082-33090.

Arcaro, A., Zvelebil, M. J., Wallasch, C., Ullrich, A., Waterfield, M. D., and Domin, J. (2000). Class II phosphoinositide 3-kinases are downstream targets of activated polypeptide growth factor receptors. Mol Cell Biol *20*, 3817-3830.

Auger, K. R., Carpenter, C. L., Shoelson, S. E., Piwnica, W. H., and Cantley, L. C. (1992). Polyoma virus middle T antigen-pp60c-src complex associates with purified phosphatidylinositol 3-kinase in vitro. J Biol Chem *267*, 5408-5415.

Auger, K. R., Serunian, L. A., Soltoff, S. P., Libby, P., and Cantley, L. C. (1989). PDGF-dependent tyrosine phosphorylation stimulates production of novel polyphosphoinositides in intact cells. Cell *57*, 167-175.

Backer, J. M., Myers, M. J., Sun, X. J., Chin, D. J., Shoelson, S. E., Miralpeix, M., and White, M. F. (1993). Association of IRS-1 with the insulin receptor and the phosphatidylinositol 3'-kinase. Formation of binary and ternary signaling complexes in intact cells. J Biol Chem *268*, 8204-8212.

Bandyopadhyay, G., Standaert, M. L., Galloway, L., Moscat, J., and Farese, R. V. (1997). Evidence for involvement of protein kinase C (PKC)-zeta and noninvolvement of diacylglycerol-sensitive PKCs in insulin-stimulated glucose transport in L6 myotubes. Endocrinology *138*, 4721-4731.

Barroso, I., Luan, J., Middelberg, R. P., Harding, A. H., Franks, P. W., Jakes, R. W., Clayton, D., Schafer, A. J., O'Rahilly, S., and Wareham, N. J. (2003). Candidate Gene Association Study in Type 2 Diabetes Indicates a Role for Genes Involved in beta-Cell Function as Well as Insulin Action. PLoS Biol *1*, E20.

Basu, A., Basu, R., Shah, P., Vella, A., Johnson, C. M., Jensen, M., Nair, K. S., Schwenk, W. F., and Rizza, R. A. (2001). Type 2 diabetes impairs splanchnic uptake of glucose but does not alter intestinal glucose absorption during enteral glucose feeding: additional evidence for a defect in hepatic glucokinase activity. Diabetes *50*, 1351-1362.

Bazenet, C. E., and Kazlauskas, A. (1994). The PDGF receptor alpha subunit activates p21ras and triggers DNA synthesis without interacting with rasGAP. Oncogene *9*, 517-525.

Beeton, C. A., Chance, E. M., Foukas, L. C., and Shepherd, P. R. (2000). Comparison of the kinetic properties of the lipid- and protein-kinase activities of the p110alpha and p110beta catalytic subunits of class-Ia phosphoinositide 3-kinases. Biochem J *350 Pt 2*, 353-359.

Bi, L., Okabe, I., Bernard, D. J., and Nussbaum, R. L. (2002). Early embryonic lethality in mice deficient in the p110beta catalytic subunit of PI 3-kinase. Mamm Genome *13*, 169-172.

Bi, L., Okabe, I., Bernard, D. J., Wynshaw-Boris, A., and Nussbaum, R. L. (1999). Proliferative defect and embryonic lethality in mice homozygous for a deletion in the p110alpha subunit of phosphoinositide 3-kinase. J Biol Chem *274*, 10963-10968.

Bluher, M., Kahn, B. B., and Kahn, C. R. (2003). Extended longevity in mice lacking the insulin receptor in adipose tissue. Science *299*, 572-574.

Bokoch, G. M., Vlahos, C. J., Wang, Y., Knaus, U. G., and Traynor-Kaplan, A. E. (1996). Rac GTPase interacts specifically with phosphatidylinositol 3-kinase. Biochem J *315 (Pt 3)*, 775-779.

Bondeva, T., Pirola, L., Bulgarelli-Leva, G., Rubio, I., Wetzker, R., and Wymann, M. P. (1998). Bifurcation of lipid and protein kinase signals of PI3Kgamma to the protein kinases PKB and MAPK. Science *282*, 293-296.

Borlado, L. R., Redondo, C., Alvarez, B., Jimenez, C., Criado, L. M., Flores, J., Marcos, M. A., Martinez, A. C., Balomenos, D., and Carrera, A. C. (2000). Increased

phosphoinositide 3-kinase activity induces a lymphoproliferative disorder and contributes to tumor generation in vivo. Faseb J *14*, 895-903.

Bostrom, H., Willetts, K., Pekny, M., Leveen, P., Lindahl, P., Hedstrand, H., Pekna, M., Hellstrom, M., Gebre-Medhin, S., Schalling, M., *et al.* (1996). PDGF-A signaling is a critical event in lung alveolar myofibroblast development and alveogenesis. Cell *85*, 863-873.

Brazil, D. P., Park, J., and Hemmings, B. A. (2002). PKB binding proteins. Getting in on the Akt. Cell *111*, 293-303.

Brunn, G. J., Williams, J., Sabers, C., Wiederrecht, G., Lawrence, J. C., Jr., and Abraham, R. T. (1996). Direct inhibition of the signaling functions of the mammalian target of rapamycin by the phosphoinositide 3-kinase inhibitors, wortmannin and LY294002. Embo J *15*, 5256-5267.

Buczynski, G., Grove, B., Nomura, A., Kleve, M., Bush, J., Firtel, R. A., and Cardelli, J. (1997). Inactivation of two Dictyostelium discoideum genes, DdPIK1 and DdPIK2, encoding proteins related to mammalian phosphatidylinositide 3-kinases, results in defects in endocytosis, lysosome to postlysosome transport, and actin cytoskeleton organization. J Cell Biol *136*, 1271-1286.

Canivenc-Gansel, E., Imhof, I., Reggiori, F., Burda, P., Conzelmann, A., and Benachour, A. (1998). GPI anchor biosynthesis in yeast: phosphoethanolamine is attached to the alpha1,4-linked mannose of the complete precursor glycophospholipid. Glycobiology *8*, 761-770.

Cantley, L. C., Auger, K. R., Carpenter, C., Duckworth, B., Graziani, A., Kapeller, R., and Soltoff, S. (1991). Oncogenes and signal transduction. Cell *64*, 281-302.

Cantley, L. C., and Neel, B. G. (1999). New insights into tumor suppression: PTEN suppresses tumor formation by restraining the phosphoinositide 3-kinase/AKT pathway. Proc Natl Acad Sci U S A *96*, 4240-4245.

Carpenter, C. L., Auger, K. R., Duckworth, B. C., Hou, W. M., Schaffhausen, B., and Cantley, L. C. (1993). A tightly associated serine/threonine protein kinase regulates phosphoinositide 3-kinase activity. Mol Cell Biol *13*, 1657-1665.

Carpenter, C. L., and Cantley, L. C. (1990). Phosphoinositide kinases. Biochemistry *29*, 11147-11156.

Carpenter, C. L., Duckworth, B. C., Auger, K. R., Cohen, B., Schaffhausen, B. S., and Cantley, L. C. (1990). Purification and characterization of phosphoinositide 3-kinase from rat liver. J Biol Chem *265*, 19704-19711.

Chang, H. W., Aoki, M., Fruman, D., Auger, K. R., Bellacosa, A., Tsichlis, P. N., Cantley, L. C., Roberts, T. M., and Vogt, P. K. (1997). Transformation of chicken cells by the gene encoding the catalytic subunit of PI 3-kinase. Science *276*, 1848-1850.

Cheatham, B., Vlahos, C. J., Cheatham, L., Wang, L., Blenis, J., and Kahn, C. R. (1994). Phosphatidylinositol 3-kinase activation is required for insulin stimulation of pp70 S6 kinase, DNA synthesis, and glucose transporter translocation. Mol Cell Biol *14*, 4902-4911.

Cheng, J. Q., Godwin, A. K., Bellacosa, A., Taguchi, T., Franke, T. F., Hamilton, T. C., Tsichlis, P. N., and Testa, J. R. (1992). AKT2, a putative oncogene encoding a member of a subfamily of protein-serine/threonine kinases, is amplified in human ovarian carcinomas. Proc Natl Acad Sci U S A *89*, 9267-9271.

Cho, H., Mu, J., Kim, J. K., Thorvaldsen, J. L., Chu, Q., Crenshaw, E. B., 3rd, Kaestner, K. H., Bartolomei, M. S., Shulman, G. I., and Birnbaum, M. J. (2001a). Insulin resistance and a diabetes mellitus-like syndrome in mice lacking the protein kinase Akt2 (PKB beta). Science *292*, 1728-1731.

Cho, H., Thorvaldsen, J. L., Chu, Q., Feng, F., and Birnbaum, M. J. (2001b). Akt1/PKBalpha is required for normal growth but dispensable for maintenance of glucose homeostasis in mice. J Biol Chem *276*, 38349-38352.

Chou, M. M., Hou, W., Johnson, J., Graham, L. K., Lee, M. H., Chen, C. S., Newton, A. C., Schaffhausen, B. S., and Toker, A. (1998). Regulation of protein kinase C zeta by PI 3-kinase and PDK-1. Curr Biol *8*, 1069-1077.

Christoforidis, S., Miaczynska, M., Ashman, K., Wilm, M., Zhao, L., Yip, S. C., Waterfield, M. D., Backer, J. M., and Zerial, M. (1999). Phosphatidylinositol-3-OH kinases are Rab5 effectors. Nat Cell Biol *1*, 249-252.

Clement, S., Krause, U., Desmedt, F., Tanti, J. F., Behrends, J., Pesesse, X., Sasaki, T., Penninger, J., Doherty, M., Malaisse, W., *et al.* (2001). The lipid phosphatase SHIP2 controls insulin sensitivity. Nature *409*, 92-97.

Collado, M., Medema, R. H., Garcia-Cao, I., Dubuisson, M. L., Barradas, M., Glassford, J., Rivas, C., Burgering, B. M., Serrano, M., and Lam, E. W. (2000). Inhibition of the phosphoinositide 3-kinase pathway induces a senescence-like arrest mediated by p27Kip1. J Biol Chem *275*, 21960-21968.

Cong, L. N., Chen, H., Li, Y., Zhou, L., McGibbon, M. A., Taylor, S. I., and Quon, M. J. (1997). Physiological role of Akt in insulin-stimulated translocation of GLUT4 in transfected rat adipose cells. Mol Endocrinol *11*, 1881-1890.

Coughlin, S. R., Escobedo, J. A., and Williams, L. T. (1989). Role of phosphatidylinositol kinase in PDGF receptor signal transduction. Science *243*, 1191-1194.

Crespo, P., Schuebel, K. E., Ostrom, A. A., Gutkind, J. S., and Bustelo, X. R. (1997). Phosphotyrosine-dependent activation of Rac-1 GDP/GTP exchange by the vav proto-oncogene product. Nature *385*, 169-172.

Cross, D. A., Alessi, D. R., Cohen, P., Andjelkovich, M., and Hemmings, B. A. (1995). Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B. Nature *378*, 785-789.

Das, B., Shu, X., Day, G. J., Han, J., Krishna, U. M., Falck, J. R., and Broek, D. (2000). Control of intramolecular interactions between the pleckstrin homology and Dbl homology domains of Vav and Sos1 regulates Rac binding. J Biol Chem *275*, 15074-15081.

Datta, S. R., Dudek, H., Tao, X., Masters, S., Fu, H., Gotoh, Y., and Greenberg, M. E. (1997). Akt phosphorylation of BAD couples survival signals to the cell- intrinsic death machinery. Cell *91*, 231-241.

Dhand, R., Hiles, I., Panayotou, G., Roche, S., Fry, M. J., Gout, I., Totty, N. F., Truong, O., Vicendo, P., Yonezawa, K., and et, a. l. (1994). PI 3-kinase is a dual specificity enzyme: autoregulation by an intrinsic protein-serine kinase activity. Embo J *13*, 522-533.

Di Cristofano, A., Pesce, B., Cordon-Cardo, C., and Pandolfi, P. P. (1998). Pten is essential for embryonic development and tumour suppression. Nat Genet *19*, 348-355.

Domin, J., Pages, F., Volinia, S., Rittenhouse, S. E., Zvelebil, M. J., Stein, R. C., and Waterfield, M. D. (1997). Cloning of a human phosphoinositide 3-kinase with a C2 domain that displays reduced sensitivity to the inhibitor wortmannin. Biochem J *326*, 139-147.

Duckworth, B. C., and Cantley, L. C. (1997). Conditional inhibition of the mitogen-activated protein kinase cascade by wortmannin. Dependence on signal strength. J Biol Chem *272*, 27665-27670.

Ellson, C. D., Anderson, K. E., Morgan, G., Chilvers, E. R., Lipp, P., Stephens, L. R., and Hawkins, P. T. (2001). Phosphatidylinositol 3-phosphate is generated in phagosomal membranes. Curr Biol *11*, 1631-1635.

Escobedo, J. A., Navankasattusas, S., Kavanaugh, W. M., Milfay, D., Fried, V. A., and Williams, L. T. (1991). cDNA cloning of a novel 85 kd protein that has SH2 domains and regulates binding of PI3-kinase to the PDGF beta-receptor. Cell *65*, 75-82.

Fleming, I. N., Gray, A., and Downes, C. P. (2000). Regulation of the Rac1-specific exchange factor Tiam1 involves both phosphoinositide 3-kinase-dependent and -independent components. Biochem J *351*, 173-182.

Fruman, D. A., Cantley, L. C., and Carpenter, C. L. (1996). Structural organization and alternative splicing of the murine phosphoinositide 3-kinase p85 alpha gene. Genomics *37*, 113-121.

Fruman, D. A., Mauvais-Jarvis, F., Pollard, D. A., Yballe, C. M., Brazil, D., Bronson, R. T., Kahn, C. R., and Cantley, L. C. (2000). Hypoglycaemia, liver necrosis and perinatal death in mice lacking all isoforms of phosphoinositide 3-kinase p85 alpha. Nat Genet *26*, 379-382.

Fruman, D. A., Snapper, S. B., Yballe, C. M., Davidson, L., Yu, J. Y., Alt, F. W., and Cantley, L. C. (1999). Impaired B cell development and proliferation in absence of phosphoinositide 3-kinase p85alpha. Science *283*, 393-397.

Fukui, Y., and Hanafusa, H. (1989). Phosphatidylinositol kinase activity associates with viral p60src protein. Mol Cell Biol *9*, 1651-1658.

Funamoto, S., Milan, K., Meili, R., and Firtel, R. A. (2001). Role of phosphatidylinositol 3' kinase and a downstream pleckstrin homology domain-containing protein in controlling chemotaxis in dictyostelium. J Cell Biol *153*, 795-810.

Gao, Z., Hwang, D., Bataille, F., Lefevre, M., York, D., Quon, M. J., and Ye, J. (2002). Serine phosphorylation of insulin receptor substrate 1 by inhibitor kappa B kinase complex. J Biol Chem *277*, 48115-48121.

Gardiner, E. M., Pestonjamasp, K. N., Bohl, B. P., Chamberlain, C., Hahn, K. M., and Bokoch, G. M. (2002). Spatial and temporal analysis of Rac activation during live neutrophil chemotaxis. Curr Biol *12*, 2029-2034.

Garofalo, R. S., Orena, S. J., Rafidi, K., Torchia, A. J., Stock, J. L., Hildebrandt, A. L., Coskran, T., Black, S. C., Brees, D. J., Wicks, J. R., *et al.* (2003). Severe diabetes, age-dependent loss of adipose tissue, and mild growth deficiency in mice lacking Akt2/PKB beta. J Clin Invest *112*, 197-208.

Goldstein, B. J. (2002). Insulin resistance as the core defect in type 2 diabetes mellitus. Am J Cardiol *90*, 3G-10G.

Grabs, D., Slepnev, V. I., Songyang, Z., David, C., Lynch, M., Cantley, L. C., and De Camilli, P. (1997). The SH3 domain of amphiphysin binds the proline-rich domain of dynamin at a single site that defines a new SH3 binding consensus sequence. J Biol Chem *272*, 13419-13425.

Greene, M. W., Morrice, N., Garofalo, R. S., and Roth, R. A. (2003a). Modulation of human insulin receptor substrate-1 tyrosine phosphorylation by protein kinase Cdelta. Biochem J *Pt*.

Greene, M. W., Sakaue, H., Wang, L., Alessi, D. R., and Roth, R. A. (2003b). Modulation of insulin-stimulated degradation of human insulin receptor substrate-1 by Serine 312 phosphorylation. J Biol Chem *278*, 8199-8211.

Gu, Y., Filippi, M. D., Cancelas, J. A., Siefring, J. E., Williams, E. P., Jasti, A. C., Harris, C. E., Lee, A. W., Prabhakar, R., Atkinson, S. J., *et al.* (2003). Hematopoietic cell regulation by Rac1 and Rac2 guanosine triphosphatases. Science *302*, 445-449.

Gual, P., Gremeaux, T., Gonzalez, T., Le Marchand-Brustel, Y., and Tanti, J. F. (2003). MAP kinases and mTOR mediate insulin-induced phosphorylation of Insulin Receptor Substrate-1 on serine residues 307, 612 and 632. Diabetologia *46*, 1532-1542.

Gupta, N., Scharenberg, A. M., Fruman, D. A., Cantley, L. C., Kinet, J. P., and Long, E. O. (1999). The SH2 domain-containing inositol 5'-phosphatase (SHIP) recruits the p85 subunit of phosphoinositide 3-kinase during FcgammaRIIb1-mediated inhibition of B cell receptor signaling. J Biol Chem *274*, 7489-7494.

Han, J., Luby-Phelps, K., Das, B., Shu, X., Xia, Y., Mosteller, R. D., Krishna, U. M., Falck, J. R., White, M. A., and Broek, D. (1998). Role of substrates and products of PI 3-kinase in regulating activation of Rac-related guanosine triphosphatases by Vav. Science *279*, 558-560.

Hara, K., Yonezawa, K., Sakaue, H., Ando, A., Kotani, K., Kitamura, T., Kitamura, Y., Ueda, H., Stephens, L., Jackson, T. R., and et, a. l. (1994). 1-Phosphatidylinositol 3-kinase activity is required for insulin- stimulated glucose transport but not for RAS activation in CHO cells. Proc Natl Acad Sci U S A *91*, 7415-7419.

Harbour, J. W., and Dean, D. C. (2000). Rb function in cell-cycle regulation and apoptosis. Nat Cell Biol *2*, E65-67.

Hartley, D., and Cooper, G. M. (2002). Role of mTOR in the degradation of IRS-1: regulation of PP2A activity. J Cell Biochem *85*, 304-314.

Hartley, D., Meisner, H., and Corvera, S. (1995a). Specific association of the beta isoform of the p85 subunit of phosphatidylinositol-3 kinase with the proto-oncogene c-cbl. J Biol Chem *270*, 18260-18263.

Hartley, K. O., Gell, D., Smith, G. C., Zhang, H., Divecha, N., Connelly, M. A., Admon, A., Lees-Miller, S. P., Anderson, C. W., and Jackson, S. P. (1995b). DNA-dependent protein kinase catalytic subunit: a relative of phosphatidylinositol 3-kinase and the ataxia telangiectasia gene product. Cell *82*, 849-856.

Haugh, J. M., Codazzi, F., Teruel, M., and Meyer, T. (2000). Spatial sensing in fibroblasts mediated by 3' phosphoinositides. J Cell Biol *151*, 1269-1280.

Hawkins, P. T., Eguinoa, A., Qiu, R. G., Stokoe, D., Cooke, F. T., Walters, R., Wennstrom, S., Claesson-Welsh, L., Evans, T., Symons, M., and et al. (1995). PDGF stimulates an increase in GTP-Rac via activation of phosphoinositide 3-kinase. Curr Biol *5*, 393-403.

Hawkins, P. T., Jackson, T. R., and Stephens, L. R. (1992). Platelet-derived growth factor stimulates synthesis of PtdIns(3,4,5)P3 by activating a PtdIns(4,5)P2 3-OH kinase. Nature *358*, 157-159.

Heuchel, R., Berg, A., Tallquist, M., Ahlen, K., Reed, R. K., Rubin, K., Claesson-Welsh, L., Heldin, C. H., and Soriano, P. (1999). Platelet-derived growth factor beta receptor regulates interstitial fluid homeostasis through phosphatidylinositol-3' kinase signaling. Proc Natl Acad Sci U S A *96*, 11410-11415.

Hiles, I. D., Otsu, M., Volinia, S., Fry, M. J., Gout, I., Dhand, R., Panayotou, G., Ruiz, L. F., Thompson, A., Totty, N. F., and et, a. l. (1992). Phosphatidylinositol 3-kinase: structure and expression of the 110 kd catalytic subunit. Cell *70*, 419-429.

Hirosumi, J., Tuncman, G., Chang, L., Gorgun, C. Z., Uysal, K. T., Maeda, K., Karin, M., and Hotamisligil, G. S. (2002). A central role for JNK in obesity and insulin resistance. Nature *420*, 333-336.

Hirsch, E., Katanaev, V. L., Garlanda, C., Azzolino, O., Pirola, L., Silengo, L., Sozzani, S., Mantovani, A., Altruda, F., and Wymann, M. P. (2000). Central role for G protein-coupled phosphoinositide 3-kinase gamma in inflammation. Science *287*, 1049-1053.

Hooshmand-Rad, R., Hajkova, L., Klint, P., Karlsson, R., Vanhaesebroeck, B., Claesson-Welsh, L., and Heldin, C. H. (2000). The PI 3-kinase isoforms p110(alpha) and p110(beta) have differential roles in PDGF- and insulin-mediated signaling. J Cell Sci *113 Pt 2*, 207-214.

Hotamisligil, G. S., Shargill, N. S., and Spiegelman, B. M. (1993). Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science *259*, 87-91.

Hu, P., Mondino, A., Skolnik, E. Y., and Schlessinger, J. (1993). Cloning of a novel, ubiquitously expressed human phosphatidylinositol 3-kinase and identification of its binding site on p85. Mol Cell Biol *13*, 7677-7688.

Inabe, K., Ishiai, M., Scharenberg, A. M., Freshney, N., Downward, J., and Kurosaki, T. (2002). Vav3 modulates B cell receptor responses by regulating phosphoinositide 3-kinase activation. J Exp Med *195*, 189-200.

Innocenti, M., Frittoli, E., Ponzanelli, I., Falck, J. R., Brachmann, S. M., Di Fiore, P. P., and Scita, G. (2003). Phosphoinositide 3-kinase activates Rac by entering in a complex with Eps8, Abi1, and Sos-1. J Cell Biol *160*, 17-23.

Inukai, K., Anai, M., Van Breda, E., Hosaka, T., Katagiri, H., Funaki, M., Fukushima, Y., Ogihara, T., Yazaki, Y., Kikuchi*, et al.* (1996). A novel 55-kDa regulatory subunit for phosphatidylinositol 3-kinase structurally similar to p55PIK Is generated by alternative splicing of the p85alpha gene. J Biol Chem *271*, 5317-5320.

Inukai, K., Funaki, M., Ogihara, T., Katagiri, H., Kanda, A., Anai, M., Fukushima, Y., Hosaka, T., Suzuki, M., Shin, B. C.*, et al.* (1997). p85alpha Gene Generates Three Isoforms of Regulatory Subunit for Phosphatidylinositol 3-Kinase (PI 3-Kinase), p50alpha, p55alpha, and p85alpha, with Different PI 3-Kinase Activity Elevating Responses to Insulin. J Biol Chem *272*, 7873-7882.

Jazet, I. M., Pijl, H., and Meinders, A. E. (2003). Adipose tissue as an endocrine organ: impact on insulin resistance. Neth J Med *61*, 194-212.

Jimenez, C., Jones, D. R., Rodríguez-Viciana, P., Gonzalez-García, A., Leonardo, E., Wennström, S., von Kobbe, C., Toran, J. L., R-Borlado, L., Calvo, V.*, et al.* (1998). Identification and characterization of a new oncogene derived from the regulatory subunit of phosphoinositide 3-kinase. Embo J *17*, 743-753.

Jimenez, C., Portela, R. A., Mellado, M., Rodriguez-Frade, J. M., Collard, J., Serrano, A., Martinez, A. C., Avila, J., and Carrera, A. C. (2000). Role of the PI3K regulatory subunit in the control of actin organization and cell migration. J Cell Biol *151*, 249-262.

Joly, M., Kazlauskas, A., Fay, F. S., and Corvera, S. (1994). Disruption of PDGF receptor trafficking by mutation of its PI-3 kinase binding sites. Science *263*, 684-687.

Kaplan, D. R., Whitman, M., Schaffhausen, B., Pallas, D. C., White, M., Cantley, L., and Roberts, T. M. (1987). Common elements in growth factor stimulation and oncogenic transformation: 85 kd phosphoprotein and phosphatidylinositol kinase activity. Cell *50*, 1021-1029.

Keely, P. J., Westwick, J. K., Whitehead, I. P., Der, C. J., and Parise, L. V. (1997). Cdc42 and Rac1 induce integrin-mediated cell motility and invasiveness through PI(3)K. Nature *390*, 632-636.

Kimura, K. D., Tissenbaum, H. A., Liu, Y., and Ruvkun, G. (1997). daf-2, an insulin receptor-like gene that regulates longevity and diapause in Caenorhabditis elegans. Science *277*, 942-946.

Kiosses, W. B., Daniels, R. H., Otey, C., Bokoch, G. M., and Schwartz, M. A. (1999). A role for p21-activated kinase in endothelial cell migration. J Cell Biol *147*, 831-844.

Klinghoffer, R. A., Mueting-Nelsen, P. F., Faerman, A., Shani, M., and Soriano, P. (2001). The two PDGF receptors maintain conserved signaling in vivo despite divergent embryological functions. Mol Cell *7*, 343-354.

Kodaki, T., Woscholski, R., Hallberg, B., Rodriguez, V. P., Downward, J., and Parker, P. J. (1994). The activation of phosphatidylinositol 3-kinase by Ras. Curr Biol *4*, 798-806.

Kops, G. J., de Ruiter, N. D., De Vries-Smits, A. M., Powell, D. R., Bos, J. L., and Burgering, B. M. (1999). Direct control of the Forkhead transcription factor AFX by protein kinase B. Nature *398*, 630-634.

Kotani, K., Carozzi, A. J., Sakaue, H., Hara, K., Robinson, L. J., Clark, S. F., Yonezawa, K., James, D. E., and Kasuga, M. (1995). Requirement for phosphoinositide 3-kinase in insulin-stimulated GLUT4 translocation in 3T3-L1 adipocytes. Biochem Biophys Res Commun *209*, 343-348.

Kotani, K., Ogawa, W., Matsumoto, M., Kitamura, T., Sakaue, H., Hino, Y., Miyake, K., Sano, W., Akimoto, K., Ohno, S., and Kasuga, M. (1998). Requirement of atypical protein kinase clambda for insulin stimulation of glucose uptake but not for Akt activation in 3T3-L1 adipocytes. Mol Cell Biol *18*, 6971-6982.

Kotani, K., Yonezawa, K., Hara, K., Ueda, H., Kitamura, Y., Sakaue, H., Ando, A., Chavanieu, A., Calas, B., Grigorescu, F., and et, a. l. (1994). Involvement of phosphoinositide 3-kinase in insulin- or IGF-1-induced membrane ruffling. Embo J *13*, 2313-2321.

Kundra, V., Escobedo, J. A., Kazlauskas, A., Kim, H. K., Rhee, S. G., Williams, L. T., and Zetter, B. R. (1994). Regulation of chemotaxis by the platelet-derived growth factor receptor-beta. Nature *367*, 474-476.

Kurosu, H., Maehama, T., Okada, T., Yamamoto, T., Hoshino, S., Fukui, Y., Ui, M., Hazeki, O., and Katada, T. (1997). Heterodimeric phosphoinositide 3-kinase consisting of p85 and p110beta is synergistically activated by the betagamma subunits of G proteins and phosphotyrosyl peptide. J Biol Chem *272*, 24252-24256.

Lam, K., Carpenter, C. L., Ruderman, N. B., Friel, J. C., and Kelly, K. L. (1994). The phosphatidylinositol 3-kinase serine kinase phosphorylates IRS-1. Stimulation by insulin and inhibition by Wortmannin. J Biol Chem *269*, 20648-20652.

Leveen, P., Pekny, M., Gebre-Medhin, S., Swolin, B., Larsson, E., and Betsholtz, C. (1994). Mice deficient for PDGF B show renal, cardiovascular, and hematological abnormalities. Genes Dev *8*, 1875-1887.

Li, J., DeFea, K., and Roth, R. A. (1999). Modulation of insulin receptor substrate-1 tyrosine phosphorylation by an Akt/phosphatidylinositol 3-kinase pathway. J Biol Chem *274*, 9351-9356.

Lindahl, P., Hellstrom, M., Kalen, M., Karlsson, L., Pekny, M., Pekna, M., Soriano, P., and Betsholtz, C. (1998). Paracrine PDGF-B/PDGF-Rbeta signaling controls mesangial cell development in kidney glomeruli. Development *125*, 3313-3322.

Ling, L. E., Druker, B. J., Cantley, L. C., and Roberts, T. M. (1992). Transformation-defective mutants of polyomavirus middle T antigen associate with phosphatidylinositol 3-kinase (PI 3-kinase) but are unable to maintain wild-type levels of PI 3-kinase products in intact cells. J Virol *66*, 1702-1708.

Liu, Y. F., Paz, K., Herschkovitz, A., Alt, A., Tennenbaum, T., Sampson, S. R., Ohba, M., Kuroki, T., LeRoith, D., and Zick, Y. (2001). Insulin stimulates PKCzeta -mediated phosphorylation of insulin receptor substrate-1 (IRS-1). A self-attenuated mechanism to negatively regulate the function of IRS proteins. J Biol Chem *276*, 14459-14465.

Macara, I. G., Marinetti, G. V., and Balduzzi, P. C. (1984). Transforming protein of avian sarcoma virus UR2 is associated with phosphatidylinositol kinase activity: possible role in tumorigenesis. Proc Natl Acad Sci U S A *81*, 2728-2732.

MacDougall, L. K., Domin, J., and Waterfield, M. D. (1995). A family of phosphoinositide 3-kinases in Drosophila identifies a new mediator of signal transduction. Curr Biol *5*, 1404-1415.

Mamay, C. L., Mingo-Sion, A. M., Wolf, D. M., Molina, M. D., and Van Den Berg, C. L. (2003). An inhibitory function for JNK in the regulation of IGF-I signaling in breast cancer. Oncogene *22*, 602-614.

Marignani, P. A., and Carpenter, C. L. (2001). Vav2 is required for cell spreading. J Cell Biol *154*, 177-186.

Marte, B. M., and Downward, J. (1997). PKB/Akt: connecting phosphoinositide 3-kinase to cell survival and beyond. Trends Biochem Sci *22*, 355-358.

Mauvais-Jarvis, F., Ueki, K., Fruman, D. A., Hirshman, M. F., Sakamoto, K., Goodyear, L. J., Iannacone, M., Accili, D., Cantley, L. C., and Kahn, C. R. (2002). Reduced expression of the murine p85alpha subunit of phosphoinositide 3-kinase improves insulin signaling and ameliorates diabetes. J Clin Invest *109*, 141-149.

Meyers, R., and Cantley, L. C. (1997). Cloning and characterization of a wortmannin-sensitive human phosphatidylinositol 4-kinase. J Biol Chem *272*, 4384-4390.

Mihaylova, V. T., Borland, C. Z., Manjarrez, L., Stern, M. J., and Sun, H. (1999). The PTEN tumor suppressor homolog in Caenorhabditis elegans regulates longevity and dauer formation in an insulin receptor-like signaling pathway. Proc Natl Acad Sci U S A *96*, 7427-7432.

Missy, K., Van Poucke, V., Raynal, P., Viala, C., Mauco, G., Plantavid, M., Chap, H., and Payrastre, B. (1998). Lipid products of phosphoinositide 3-kinase interact with Rac1 GTPase and stimulate GDP dissociation. J Biol Chem *273*, 30279-30286.

Morris, J. Z., Tissenbaum, H. A., and Ruvkun, G. (1996). A phosphatidylinositol-3-OH kinase family member regulating longevity and diapause in Caenorhabditis elegans. NatureNature *382*, 536-539.

Musacchio, A., Cantley, L. C., and Harrison, S. C. (1996). Crystal structure of the breakpoint cluster region-homology domain from phosphoinositide 3-kinase p85 alpha subunit. Proc Natl Acad Sci U S A *93*, 14373-14378.

Nishimura, R., Li, W., Kashishian, A., Mondino, A., Zhou, M., Cooper, J., and Schlessinger, J. (1993). Two signaling molecules share a phosphotyrosine-containing binding site in the platelet-derived growth factor receptor. Mol Cell Biol *13*, 6889-6896.

Nobes, C., and Hall, A. (1994). Regulation and function of the Rho subfamily of small GTPases. Curr Opin Genet Dev *4*, 77-81.

Nobes, C. D., and Hall, A. (1999). Rho GTPases control polarity, protrusion, and adhesion during cell movement. J Cell Biol *144*, 1235-1244.

Nobes, C. D., Hawkins, P., Stephens, L., and Hall, A. (1995). Activation of the small GTP-binding proteins rho and rac by growth factor receptors. J Cell Sci, 225-233.

Norman, B. H., Shih, C., Toth, J. E., Ray, J. E., Dodge, J. A., Johnson, D. W., Rutherford, P. G., Schultz, R. M., Worzalla, J. F., and Vlahos, C. J. (1996). Studies on the mechanism of phosphatidylinositol 3-kinase inhibition by wortmannin and related analogs. J Med Chem *39*, 1106-1111.

Ogg, S., and Ruvkun, G. (1998). The C. elegans PTEN homolog, DAF-18, acts in the insulin receptor-like metabolic signaling pathway. Mol Cell *2*, 887-893.

Okada, T., Kawano, Y., Sakakibara, T., Hazeki, O., and Ui, M. (1994). Essential role of phosphatidylinositol 3-kinase in insulin-induced glucose transport and antilipolysis in rat adipocytes. Studies with a selective inhibitor wortmannin. J Biol Chem *269*, 3568-3573.

Ozes, O. N., Akca, H., Mayo, L. D., Gustin, J. A., Maehama, T., Dixon, J. E., and Donner, D. B. (2001). A phosphatidylinositol 3-kinase/Akt/mTOR pathway mediates and PTEN antagonizes tumor necrosis factor inhibition of insulin signaling through insulin receptor substrate-1. Proc Natl Acad Sci U S A *98*, 4640-4645.

Paradis, S., and Ruvkun, G. (1998). Caenorhabditis elegans Akt/PKB transduces insulin receptor-like signals from AGE-1 PI3 kinase to the DAF-16 transcription factor. Genes Dev *12*, 2488-2498.

Park, C. S., Schneider, I. C., and Haugh, J. M. (2003). Kinetic analysis of platelet-derived growth factor receptor/phosphoinositide 3-kinase/Akt signaling in fibroblasts. J Biol Chem *278*, 37064-37072.

Philp, A. J., Campbell, I. G., Leet, C., Vincan, E., Rockman, S. P., Whitehead, R. H., Thomas, R. J., and Phillips, W. A. (2001). The phosphatidylinositol 3'-kinase p85alpha gene is an oncogene in human ovarian and colon tumors. Cancer Res *61*, 7426-7429.

Pleiman, C. M., Hertz, W. M., and Cambier, J. C. (1994). Activation of phosphatidylinositol-3' kinase by Src-family kinase SH3 binding to the p85 subunit. Science *263*, 1609-1612.

Pons, S., Asano, T., Glasheen, E., Miralpeix, M., Zhang, Y., Fisher, T. L., Myers, M. G., Jr., Sun, X. J., and White, M. F. (1995). The structure and function of p55PIK reveal a new regulatory subunit for phosphatidylinositol 3-kinase. Mol Cell Biol *15*, 4453-4465.

Quon, M. J., Chen, H., Ing, B. L., Liu, M.-L., Zarnowski, M. J., Yonezawa, K., M., K., Cushman, S. W., and Taylor, S. I. (1995). Roles of 1-Phosphatidylinositol 3-kinase and ras in regulating translocation of GLUT 4 in transfected rat adipose cells. Mol Cell Biol *15*, 5403-5411.

Reif, K., Nobes, C. D., Thomas, G., Hall, A., and Cantrell, D. A. (1996). Phosphatidylinositol 3-kinase signals activate a selective subset of Rac/Rho-dependent effector pathways. Curr Biol *6*, 1445-1455.

Remillard, B., Petrillo, R., Maslinski, W., Tsudo, M., Strom, T. B., Cantley, L., and Varticovski, L. (1991). Interleukin-2 receptor regulates activation of phosphatidylinositol 3- kinase. J Biol Chem *266*, 14167-14170.

Rickert, P., Weiner, O. D., Wang, F., Bourne, H. R., and Servant, G. (2000). Leukocytes navigate by compass: roles of PI3Kgamma and its lipid products. Trends Cell Biol *10*, 466-473.

Ricort, J. M., Tanti, J. F., Van Obberghen, E., and Le Marchand-Brustel, Y. (1995). Alterations in insulin signalling pathway induced by prolonged insulin treatment of 3T3-L1 adipocytes. Diabetologia *38*, 1148-1156.

Ridley, A. (1999). Rac and Rho. Curr Biol *9*, R156.

Ridley, A. J., and Hall, A. (1992). The Small GTP-Binding Protein rho Regulates the Assembly of Focal Adhesions and Actin Stress Fibers in Response to Growth Factors. Cell *70*, 389-399.

Ridley, A. J., Paterson, H. F., Johnston, C. L., Diekmann, D., and Hall, A. (1992). The small GTP-binding protein rac regulates growth factor-induced membrane ruffling. Cell *70*, 401-410.

Roche, S., Downward, J., Raynal, P., and Courtneidge, S. A. (1998). A function for phosphatidylinositol 3-kinase beta (p85alpha-p110beta) in fibroblasts during mitogenesis: requirement for insulin- and lysophosphatidic acid-mediated signal transduction. Mol Cell Biol *18*, 7119-7129.

Rodriguez-Viciana, P., Warne, P. H., Vanhaesebroeck, B., Waterfield, M. D., and Downward, J. (1996). Activation of phosphoinositide 3-kinase by interaction with Ras and by point mutation. Embo J *15*, 2442-2451.

Romashkova, J. A., and Makarov, S. S. (1999). NF-kappaB is a target of AKT in anti-apoptotic PDGF signalling. Nature *401*, 86-90.

Rosenkranz, S., DeMali, K. A., Gelderloos, J. A., Bazenet, C., and Kazlauskas, A. (1999). Identification of the receptor-associated signaling enzymes that are required for platelet-derived growth factor-AA-dependent chemotaxis and DNA synthesis [In Process Citation]. J Biol Chem *274*, 28335-28343.

Rouault, J. P., Kuwabara, P. E., Sinilnikova, O. M., Duret, L., Thierry-Mieg, D., and Billaud, M. (1999). Regulation of dauer larva development in Caenorhabditis elegans by daf-18, a homologue of the tumour suppressor PTEN. Curr Biol *9*, 329-332.

Ruderman, N. B., Kapeller, R., White, M. F., and Cantley, L. C. (1990). Activation of phosphatidylinositol 3-kinase by insulin. Proc Natl Acad Sci U S A *87*, 1411-1415.

Rui, L., Aguirre, V., Kim, J. K., Shulman, G. I., Lee, A., Corbould, A., Dunaif, A., and White, M. F. (2001). Insulin/IGF-1 and TNF-alpha stimulate phosphorylation of IRS-1 at inhibitory Ser307 via distinct pathways. J Clin Invest *107*, 181-189.

Rupper, A. C., Rodriguez-Paris, J. M., Grove, B. D., and Cardelli, J. A. (2001). p110-related PI 3-kinases regulate phagosome-phagosome fusion and phagosomal pH through a PKB/Akt dependent pathway in Dictyostelium. J Cell Sci *114*, 1283-1295.

Sachdev, P., Zeng, L., and Wang, L. H. (2002). Distinct role of phosphatidylinositol 3-kinase and Rho family GTPases in Vav3-induced cell transformation, cell motility, and morphological changes. J Biol Chem *277*, 17638-17648.

Sadhu, C., Masinovsky, B., Dick, K., Sowell, C. G., and Staunton, D. E. (2003). Essential role of phosphoinositide 3-kinase delta in neutrophil directional movement. J Immunol *170*, 2647-2654.

Sanjay, A., Horne, W. C., and Baron, R. (2001). The Cbl family: ubiquitin ligases regulating signaling by tyrosine kinases. Sci STKE *2001*, PE40.

Scita, G., Nordstrom, J., Carbone, R., Tenca, P., Giardina, G., Gutkind, S., Bjarnegard, M., Betsholtz, C., and Di Fiore, P. P. (1999). EPS8 and E3B1 transduce signals from Ras to Rac. Nature *401*, 290-293.

Scita, G., Tenca, P., Areces, L. B., Tocchetti, A., Frittoli, E., Giardina, G., Ponzanelli, I., Sini, P., Innocenti, M., and Di Fiore, P. P. (2001). An effector region in Eps8 is responsible for the activation of the Rac-specific GEF activity of Sos-1 and for the proper localization of the Rac-based actin-polymerizing machine. J Cell Biol *154*, 1031-1044.

Serunian, L. A., Auger, K. R., Roberts, T. M., and Cantley, L. C. (1990). Production of novel polyphosphoinositides in vivo is linked to cell transformation by polyomavirus middle T antigen. J Virol *64*, 4718-4725.

Serunian, L. A., Haber, M. T., Fukui, T., Kim, J. W., Rhee, S. G., Lowenstein, J. M., and Cantley, L. C. (1989). Polyphosphoinositides produced by phosphatidylinositol 3-kinase are poor substrates for phospholipases C from rat liver and bovine brain. J Biol Chem *264*, 17809-17815.

Severinsson, L., Ek, B., Mellstrom, K., Claesson-Welsh, L., and Heldin, C.-H. (1990). Deletion of the kinase insert sequence of the platelet-derived growth factor b-receptor affects receptor kinase activity and signal transduction. Mol Cell Biol *10*, 801-809.

Shayesteh, L., Lu, Y., Kuo, W. L., Baldocchi, R., Godfrey, T., Collins, C., Pinkel, D., Powell, B., Mills, G. B., and Gray, J. W. (1999). PIK3CA is implicated as an oncogene in ovarian cancer [see comments]. Nat Genet *21*, 99-102.

Shi, S. H., Jan, L. Y., and Jan, Y. N. (2003). Hippocampal neuronal polarity specified by spatially localized mPar3/mPar6 and PI 3-kinase activity. Cell *112*, 63-75.

Shinohara, M., Terada, Y., Iwamatsu, A., Shinohara, A., Mochizuki, N., Higuchi, M., Gotoh, Y., Ihara, S., Nagata, S., Itoh, H., *et al.* (2002). SWAP-70 is a guanine-nucleotide-exchange factor that mediates signalling of membrane ruffling. Nature *416*, 759-763.

Siddhanta, U., McIlroy, J., Shah, A., Zhang, Y., and Backer, J. M. (1998). Distinct roles for the p110alpha and hVPS34 phosphatidylinositol 3'-kinases in vesicular trafficking, regulation of the actin cytoskeleton, and mitogenesis. J Cell Biol *143*, 1647-1659.

Skolnik, E. Y., Margolis, B., Mohammadi, M., Lowenstein, E., Fischer, R., Drepps, A., Ullrich, A., and Schlessinger, J. (1991). Cloning of PI3 kinase-associated p85 utilizing a novel method for expression/cloning of target proteins for receptor tyrosine kinases. Cell *65*, 83-90.

Soltoff, S. P., and Cantley, L. C. (1996). p120cbl is a cytosolic adapter protein that associates with phosphoinositide 3-kinase in response to epidermal growth factor in PC12 and other cells. J Biol Chem *271*, 563-567.

Songyang, Z., Shoelson, S. E., Chaudhuri, M., Gish, G., Pawson, T., Haser, W. G., King, F., Roberts, T., Ratnofsky, S., Lechleider, R. J., and et al. (1993). SH2 domains recognize specific phosphopeptide sequences. Cell *72*, 767-778.

Soriano, P. (1994). Abnormal kidney development and hematological disorders in PDGF beta-receptor mutant mice. Genes Dev *8*, 1888-1896.

Soriano, P. (1997). The PDGF alpha receptor is required for neural crest cell development and for normal patterning of the somites. Development *124*, 2691-2700.

Srinivasan, S., Wang, F., Glavas, S., Ott, A., Hofmann, F., Aktories, K., Kalman, D., and Bourne, H. R. (2003). Rac and Cdc42 play distinct roles in regulating PI(3,4,5)P3 and polarity during neutrophil chemotaxis. J Cell Biol *160*, 375-385.

Stambolic, V., Suzuki, A., de la Pompa, J. L., Brothers, G. M., Mirtsos, C., Sasaki, T., Ruland, J., Penninger, J. M., Siderovski, D. P., and Mak, T. W. (1998). Negative regulation of PKB/Akt-dependent cell survival by the tumor suppressor PTEN. Cell *95*, 29-39.

Stephens, L., Ellson, C., and Hawkins, P. (2002). Roles of PI3Ks in leukocyte chemotaxis and phagocytosis. Curr Opin Cell Biol *14*, 203-213.

Stoyanova, S., Bulgarelli-Leva, G., Kirsch, C., Hanck, T., Klinger, R., Wetzker, R., and Wymann, M. P. (1997). Lipid kinase and protein kinase activities of G-protein-coupled phosphoinositide 3-kinase gamma: structure-activity analysis and interactions with wortmannin. Biochem J *324*, 489-495.

Sugimoto, Y., Whitman, M., Cantley, L. C., and Erikson, R. L. (1984). Evidence that the Rous sarcoma virus transforming gene product phosphorylates phosphatidylinositol and diacylglycerol. Proc Natl Acad Sci U S A *81*, 2117-2121.

Sun, M., Wang, G., Paciga, J. E., Feldman, R. I., Yuan, Z. Q., Ma, X. L., Shelley, S. A., Jove, R., Tsichlis, P. N., Nicosia, S. V., and Cheng, J. Q. (2001). AKT1/PKBalpha kinase is frequently elevated in human cancers and its constitutive activation is required for oncogenic transformation in NIH3T3 cells. Am J Pathol *159*, 431-437.

Tamas, P., Solti, Z., Bauer, P., Illes, A., Sipeki, S., Bauer, A., Farago, A., Downward, J., and Buday, L. (2003). Mechanism of epidermal growth factor regulation of Vav2, a guanine nucleotide exchange factor for Rac. J Biol Chem *278*, 5163-5171.

Tang, Y., Zhou, H., Chen, A., Pittman, R. N., and Field, J. (2000). The Akt proto-oncogene links Ras to Pak and cell survival signals. J Biol Chem *275*, 9106-9109.

Terauchi, Y., Tsuji, Y., Satoh, S., Minoura, H., Murakami, K., Okuno, A., Inukai, K., Asano, T., Kaburagi, Y., Ueki, K., *et al.* (1999). Increased insulin sensitivity and hypoglycaemia in mice lacking the p85 alpha subunit of phosphoinositide 3-kinase. Nat Genet *21*, 230-235.

Tissenbaum, H. A., and Ruvkun, G. (1998). An insulin-like signaling pathway affects both longevity and reproduction in Caenorhabditis elegans. Genetics *148*, 703-717.

Toker, A., Bachelot, C., Chen, C.-S., Falck, J. R., Hartwig, J. H., Cantley, L. C., and Kovacsovics, T. (1995). Phosphorylation of the p47 platelet phosphoprotein is mediated by the lipid products of phosphoinositide 3-kinase. J Biol Chem *270*, 29525-29531.

Toker, A., and Cantley, L. C. (1997). Signalling through the lipid products of phosphoinositide-3-OH kinase. Nature *387*, 673-676.

Toker, A., and Newton, A. C. (2000). Akt/protein kinase B is regulated by autophosphorylation at the hypothetical PDK-2 site. J Biol Chem *275*, 8271-8274.

Tolias, K. F., Cantley, L. C., and Carpenter, C. L. (1995). Rho family GTPases bind to phosphoinositide kinases. J Biol Chem *270*, 17656-17659.

Ueki, K., Fruman, D. A., Brachmann, S. M., Tseng, Y. H., Cantley, L. C., and Kahn, C. R. (2002a). Molecular balance between the regulatory and catalytic subunits of phosphoinositide 3-kinase regulates cell signaling and survival. Mol Cell Biol *22*, 965-977.

Ueki, K., Fruman, D. A., Yballe, C. M., Fassaur, M., Klein, J., Asano, T., Cantley, L. C., and Kahn, C. R. (2003). Positive and negative roles of p85alpha and p85beta regulatory subunits of phosphoinositide 3-kinase in insulin signaling. J Biol Chem.

Ueki, K., Yballe, C. M., Brachmann, S. M., Vicent, D., Watt, J. M., Kahn, C. R., and Cantley, L. C. (2002b). Increased insulin sensitivity in mice lacking p85beta subunit of phosphoinositide 3-kinase. Proc Natl Acad Sci U S A *99*, 419-424.

Uysal, K. T., Wiesbrock, S. M., Marino, M. W., and Hotamisligil, G. S. (1997). Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. Nature *389*, 610-614.

Valius, M., and Kazlauskas, A. (1993). Phospholipase C-gamma 1 and phosphatidylinositol 3 kinase are the downstream mediators of the PDGF receptor's mitogenic signal. Cell *73*, 321-334.

Vanhaesebroeck, B., Leevers, S. J., Panayotou, G., and Waterfield, M. D. (1997a). Phosphoinositide 3-kinases: a conserved family of signal transducers. Trends Biochem SciTrends Biochem Sci *22*, 267-272.

Vanhaesebroeck, B., Welham, M. J., Kotani, K., Stein, R., Warne, P. H., Zvelebil, M. J., Higashi, K., Volinia, S., Downward, J., and Waterfield, M. D. (1997b). P110delta, a novel phosphoinositide 3-kinase in leukocytes. Proc Natl Acad Sci U S A *94*, 4330-4335.
Varticovski, L., Daley, G. Q., Jackson, P., Baltimore, D., and Cantley, L. C. (1991). Activation of phosphatidylinositol 3-kinase in cells expressing abl oncogene variants. Mol Cell Biol *11*, 1107-1113.

Varticovski, L., Druker, B., Morrison, D., Cantley, L., and Roberts, T. (1989). The colony stimulating factor-1 receptor associates with and activates phosphatidylinositol-3 kinase. Nature *342*, 699-702.

Vieira, O. V., Botelho, R. J., Rameh, L., Brachmann, S. M., Matsuo, T., Davidson, H. W., Schreiber, A., Backer, J. M., Cantley, L. C., and Grinstein, S. (2001). Distinct roles of class I and class III phosphatidylinositol 3-kinases in phagosome formation and maturation. J Cell Biol *155*, 19-25.

Vlahos, C. J., Matter, W. F., Hui, K. Y., and Brown, R. F. (1994). A specific inhibitor of phosphatidylinositol 3-kinase, 2-(4- morpholinyl)-8-phenyl-4H-1-benzopyran-4-one (LY294002). J Biol Chem *269*, 5241-5248.

Weiner, O. D., Neilsen, P. O., Prestwich, G. D., Kirschner, M. W., Cantley, L. C., and Bourne, H. R. (2002). A PtdInsP(3)- and Rho GTPase-mediated positive feedback loop regulates neutrophil polarity. Nat Cell Biol *4*, 509-513.

Weinkove, D., Leevers, S. J., MacDougall, L. K., and Waterfield, M. D. (1997). p60 is an adaptor for the Drosophila phosphoinositide 3-kinase, Dp110. J Biol Chem *272*, 14606-14610.

Welch, H. C., Coadwell, W. J., Ellson, C. D., Ferguson, G. J., Andrews, S. R., Erdjument-Bromage, H., Tempst, P., Hawkins, P. T., and Stephens, L. R. (2002). P-Rex1, a PtdIns(3,4,5)P3- and Gbetagamma-regulated guanine-nucleotide exchange factor for Rac. Cell *108*, 809-821.

Wennstrom, S., Hawkins, P., Cooke, F., Hara, K., Yonezawa, K., Kasuga, M., Jackson, T., Claesson, W. L., and Stephens, L. (1994a). Activation of phosphoinositide 3-kinase is required for PDGF- stimulated membrane ruffling. Curr Biol *4*, 385-393.

Wennstrom, S., Siegbahn, A., Yokote, K., Arvidsson, A. K., Heldin, C. H., Mori, S., and Claesson-Welsh, L. (1994b). Membrane ruffling and chemotaxis transduced by the PDGF beta-receptor require the binding site for phosphatidylinositol 3' kinase. Oncogene *9*, 651-660.

Whitman, M., Downes, C. P., Keeler, M., Keller, T., and Cantley, L. (1988). Type I phosphatidylinositol kinase makes a novel inositol phospholipid, phosphatidylinositol-3-phosphate. Nature *332*, 644-646.

Whitman, M., Kaplan, D. R., Schaffhausen, B., Cantley, L., and Roberts, T. M. (1985). Association of phosphatidylinositol kinase activity with polyoma middle-T competent for transformation. Nature *315*, 239-242.

Wymann, M. P., Bulgarelli-Leva, G., Zvelebil, M. J., Pirola, L., Vanhaesebroeck, B., Waterfield, M. D., and Panayotou, G. (1996). Wortmannin inactivates phosphoinositide

3-kinase by covalent modification of Lys-802, a residue involved in the phosphate transfer reaction. Mol Cell Biol *16*, 1722-1733.

Yamauchi, T., Kamon, J., Minokoshi, Y., Ito, Y., Waki, H., Uchida, S., Yamashita, S., Noda, M., Kita, S., Ueki, K., *et al.* (2002). Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med *8*, 1288-1295.

Yoshii, S., Tanaka, M., Otsuki, Y., Wang, D. Y., Guo, R. J., Zhu, Y., Takeda, R., Hanai, H., Kaneko, E., and Sugimura, H. (1999). alphaPIX nucleotide exchange factor is activated by interaction with phosphatidylinositol 3-kinase. Oncogene *18*, 5680-5690.

Yu, J., Zhang, Y., McIlroy, J., Rordorf-Nikolic, T., Orr, G. A., and Backer, J. M. (1998). Regulation of the p85/p110 phosphatidylinositol 3'-kinase: stabilization and inhibition of the p110alpha catalytic subunit by the p85 regulatory subunit. Mol Cell Biol *18*, 1379-1387.

Zheng, Y., Bagrodia, S., and Cerione, R. A. (1994). Activation of phosphoinositide 3-kinase activity by Cdc42Hs binding to p85. J Biol Chem *269*, 18727-18730.

Zhou, G. L., Zhuo, Y., King, C. C., Fryer, B. H., Bokoch, G. M., and Field, J. (2003). Akt phosphorylation of serine 21 on Pak1 modulates Nck binding and cell migration. Mol Cell Biol *23*, 8058-8069.

Zhou, K., Takegawa, K., Emr, S. D., and Firtel, R. A. (1995). A phosphatidylinositol (PI) kinase gene family in Dictyostelium discoideum: biological roles of putative mammalian p110 and yeast Vps34p PI 3-kinase homologs during growth and development. Mol Cell Biol *15*, 5645-5656.

Zick, Y. (2001). Insulin resistance: a phosphorylation-based uncoupling of insulin signaling. Trends Cell Biol *11*, 437-441.