

References

- Ahmad T., Eisen T. 2004 Kinase inhibition with BAY 43-9006 in renal cell carcinoma. *Clin Cancer Res.* 10(18 Pt 2):6388S-92S.
- Anjum R., Roux P.P., Ballif B.A., Gygi S.P., Blenis J. 2005 The tumor suppressor DAP kinase is a target of RSK-mediated survival signaling. *Curr Biol.* 15(19):1762-7.
- Almeida A., Moncada S., Bolaños J.P. 2004 Nitric oxide switches on glycolysis through the AMP protein kinase and 6-phosphofructo-2-kinase pathway. *Nat Cell Biol.* 6(1):45-51.
- Araki M., Motojima K. 2006 Identification of ERRalpha as a specific partner of PGC-1alpha for the activation of PDK4 gene expression in muscle. *FEBS J.* 273(8):1669-80.
- Askonas L.J., Ricigliano J.W., Penning T.M. 1991 The kinetic mechanism catalysed by homogeneous rat liver 3 alpha-hydroxysteroid dehydrogenase. Evidence for binary and ternary dead-end complexes containing non-steroidal anti-inflammatory drugs. *Biochem J.* 278 (Pt 3):835-41.
- Astuti D., Latif F., Dallol A., Dahia P.L., Douglas F., George E., Sköldbberg F., Husebye E.S., Eng C., Maher E.R. 2001 Gene mutations in the succinate dehydrogenase subunit SDHB cause susceptibility to familial pheochromocytoma and to familial paraganglioma. *Am J Hum Genet.* 69(1):49-54.
- Atsumi T., Chesney J., Metz C., Leng L., Donnelly S., Makita Z., Mitchell R., Bucala R. 2002 High expression of inducible 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (iPFK-2; PFKFB3) in human cancers. *Cancer Res.* 62(20):5881-7
- Averous J., Fonseca B.D., Proud C.G. 2008 Regulation of cyclin D1 expression by mTORC1 signaling requires eukaryotic initiation factor 4E-binding protein 1. *Oncogene.* 27(8):1106-13.

Baas A.F., Boudeau J., Sapkota G.P., Smit L., Medema R., Morrice N.A., Alessi D.R., Clevers H.C. 2003 Activation of the tumour suppressor kinase LKB1 by the STE20-like pseudokinase STRAD. *EMBO J.* 22(12):3062-72.

Baas A.F., Kuipers J., van der Wel N.N., Batlle E., Koerten H.K., Peters P.J., Clevers H.C. 2004 Complete polarization of single intestinal epithelial cells upon activation of LKB1 by STRAD. *Cell.* 116(3):457-66.

Balss J., Meyer J., Mueller W., Korshunov A., Hartmann C., von Deimling A. 2008 Analysis of the IDH1 codon 132 mutation in brain tumors. *Acta Neuropathol.* 116(6):597-602.

Bardeesy N., Sinha M., Hezel A.F., Signoretti S., Hathaway N.A., Sharpless N.E., Loda M., Carrasco D.R., DePinho R.A. 2002 Loss of the Lkb1 tumour suppressor provokes intestinal polyposis but resistance to transformation. *Nature.* 419(6903):162-7.

Barski O.A., Tipparaju S.M., Bhatnagar A. 2008 The aldo-keto reductase superfamily and its role in drug metabolism and detoxification. *Drug Metab Rev.* 40(4):553-624.

Baysal B.E., Ferrell R.E., Willett-Brozick J.E., Lawrence E.C., Myssiorek D, Bosch A., van der Mey A., Taschner P.E., Rubinstein W.S., Myers E.N., Richard C.W. 3rd., Cornelisse C.J., Devilee P., Devlin B. 2000 Mutations in SDHD, a mitochondrial complex II gene, in hereditary paraganglioma. *Science.* 287(5454):848-51

Bell D.W., Gore I., Okimoto R.A., Godin-Heymann N., Sordella R., Mulloy R., Sharma S.V., Brannigan B.W., Mohapatra G., Settleman J., Haber D.A. 2005 Inherited susceptibility to lung cancer may be associated with the T790M drug resistance mutation in EGFR. *Nat Genet.* 37(12):1315-6.

Bergeron R., Ren J.M., Cadman K.S., Moore I.K., Perret P., Pypaert M., Young L.H., Semenkovich C.F., Shulman G.I. 2001 Chronic activation of AMP kinase results in NRF-1 activation and mitochondrial biogenesis. *Am J Physiol Endocrinol Metab.* 281(6):E1340-6.

Bessard A., Frémin C., Ezan F., Coutant A., Baffet G. 2007 MEK/ERK-dependent uPAR expression is required for motility via phosphorylation of P70S6K in human hepatocarcinoma cells. *J Cell Physiol.* 212(2):526-36.

Bhandari B.K., Feliars D., Duraisamy S., Stewart J.L., Gingras A.C., Abboud H.E., Choudhury G.G., Sonenberg N., Kasinath B.S. 2001 Insulin regulation of protein translation repressor 4E-BP1, an eIF4E-binding protein, in renal epithelial cells. *Kidney Int.* 59(3):866-75.

Bignell G.R., Barfoot R., Seal S., Collins N., Warren W., Stratton M.R. 1998 Low frequency of somatic mutations in the LKB1/Peutz-Jeghers syndrome gene in sporadic breast cancer. *Cancer Res.* 58(7):1384-6

Bleeker F.E., Lamba S., Leenstra S., Troost D., Hulsebos T., Vandertop W.P., Frattini M., Molinari F., Knowles M., Cerrato A., Rodolfo M., Scarpa A., Felicioni L., Buttitta F., Malatesta S., Marchetti A., Bardelli A. 2009 IDH1 mutations at residue p.R132 (IDH1(R132)) occur frequently in high-grade gliomas but not in other solid tumors. *Hum Mutat.* 30(1):7-11.

Blumenschein G. Jr. 2008 Sorafenib in lung cancer: clinical developments and future directions. *J Thorac Oncol.* 3(6 Suppl 2):S124-7.

Board M., Humm S., Newsholme E.A. 1990 Maximum activities of key enzymes of glycolysis, glutaminolysis, pentose phosphate pathway and tricarboxylic acid cycle in normal, neoplastic and suppressed cells. *Biochem J.* 265(2):503-9.

Boardman L.A., Couch F.J., Burgart L.J., Schwartz D., Berry R., McDonnell S.K., Schaid D.J., Hartmann L.C., Schroeder J.J., Stratakis C.A., Thibodeau S.N. 2000 Genetic heterogeneity in Peutz-Jeghers syndrome. *Hum Mutat.* 16(1):23-30.

Bonni A., Brunet A., West A.E., Datta S.R., Takasu M.A., Greenberg M.E. 1999 Cell survival promoted by the Ras-MAPK signaling pathway by transcription-dependent and -independent mechanisms. *Science.* 286(5443):1358-62.

Bolstad B.M., Irizarry R.A., Astrand M., Speed T.P. 2003 A comparison of normalization methods for high density oligonucleotide array data based on variance and bias. *Bioinformatics.* 19(2):185-93.

- Bos J.L. 1989 ras oncogenes in human cancer: a review. *Cancer Res.* 9(17):4682-9.
- Boudeau J., Baas A.F., Deak M., Morrice N.A., Kieloch A., Schutkowski M., Prescott A.R., Clevers H.C., Alessi D.R. 2003 MO25alpha/beta interact with STRADalpha/beta enhancing their ability to bind, activate and localize LKB1 in the cytoplasm. *EMBO J.* 22(19):5102-14.
- Boudeau J., Scott J.W., Resta N., Deak M., Kieloch A., Komander D., Hardie D.G., Prescott A.R., van Aalten D.M., Alessi D.R. 2004 Analysis of the LKB1-STRAD-MO25 complex. *J Cell Sci.* 117(Pt 26):6365-75.
- Brajenovic M., Joberty G., Küster B., Bouwmeester T., Drewes G. 2004 Comprehensive proteomic analysis of human Par protein complexes reveals an interconnected protein network *J Biol Chem.* 279(13):12804-11.
- Brose M.S., Volpe P., Feldman M., Kumar M., Rishi I., Gerrero R., Einhorn E., Herlyn M., Minna J., Nicholson A., Roth J.A., Albelda S.M., Davies H., Cox C., Brignell G., Stephens P., Futreal P.A., Wooster R., Stratton M.R., Weber B.L. 2002 BRAF and RAS mutations in human lung cancer and melanoma. *Cancer Res.* 62(23):6997-7000.
- Brown E.J., Beal P.A., Keith C.T., Chen J., Shin T.B., Schreiber S.L. 1995 Control of p70 s6 kinase by kinase activity of FRAP in vivo. *Nature.* 377(6548):441-6.
- Brown R.S., Wahl R.L. 1993 Overexpression of Glut-1 glucose transporter in human breast cancer. An immunohistochemical study. *Cancer.* 72(10):2979-85
- Brunn G.J., Hudson C.C., Sekulić A., Williams J.M., Hosoi H., Houghton P.J., Lawrence J.C. Jr., Abraham R.T. 1997 Phosphorylation of the translational repressor PHAS-I by the mammalian target of rapamycin. *Science.* 277(5322):99-101.
- Buday L., Downward J. 1993 Epidermal growth factor regulates p21ras through the formation of a complex of receptor, Grb2 adapter protein, and Sos nucleotide exchange factor. *Cell.* 73(3):611-20

Budihardjo I.I., Walker D.L., Svingen P.A., Buckwalter C.A., Desnoyers S., Eckdahl S., Shah G.M., Poirier G.G., Reid J.M., Ames M.M., Kaufmann S.H. 1998 6-Aminonicotinamide sensitizes human tumor cell lines to cisplatin. *Clin Cancer Res.* 4(1):117-30.

Bunney T.D., Harris R., Gandarillas N.L., Josephs M.B., Roe S.M., Sorli S.C., Paterson H.F., Rodrigues-Lima F., Esposito D., Ponting C.P., Gierschik P., Pearl L.H., Driscoll P.C., Katan M. 2006 Structural and mechanistic insights into ras association domains of phospholipase C epsilon. *Mol Cell.* 21(4):495-507.

Cantó C., Gerhart-Hines Z., Feige J.N., Lagouge M., Noriega L., Milne J.C., Elliott P.J., Puigserver P., Auwerx J. 2009 AMPK regulates energy expenditure by modulating NAD⁺ metabolism and SIRT1 activity. *Nature.* 458(7241):1056-60.

Cao D., Fan S.T., Chung S.S. 1998 Identification and characterization of a novel human aldose reductase-like gene. *J Biol Chem.* 273(19):11429-35.

Capon D.J., Seeburg P.H., McGrath J.P., Hayflick J.S., Edman U., Levinson A.D., Goeddel D.V. 1983 Activation of Ki-ras2 gene in human colon and lung carcinomas by two different point mutations. *Nature.* 304(5926):507-13.

Carling D., Zammit V.A., Hardie D.G. 1987 A common bicyclic protein kinase cascade inactivates the regulatory enzymes of fatty acid and cholesterol biosynthesis. *FEBS Lett.* 223(2):217-22

Carling D., Clarke P.R., Zammit V.A., Hardie D.G. 1989 Purification and characterization of the AMP-activated protein kinase. Copurification of acetyl-CoA carboxylase kinase and 3-hydroxy-3-methylglutaryl-CoA reductase kinase activities *Eur J Biochem.* 186(1-2):129-36.

Carretero J., Medina P.P., Blanco R., Smit L., Tang M., Roncador G., Maestre L., Conde E., Lopez-Rios F., Clevers H.C., Sanchez-Cespedes M. 2007 Dysfunctional AMPK activity, signalling through mTOR and survival in response to energetic stress in LKB1-deficient lung cancer. *Oncogene.* 26(11):1616-25.

Carrière A., Cargnello M., Julien L.A., Gao H., Bonneil E., Thibault P., Roux P.P. 2008 Oncogenic MAPK signaling stimulates mTORC1 activity by promoting RSK-mediated raptor phosphorylation. *Curr Biol.* 18(17):1269-77.

Chang E.H., Gonda M.A., Ellis R.W., Scolnick E.M., Lowy D.R. 1982 Human genome contains four genes homologous to transforming genes of Harvey and Kirsten murine sarcoma viruses. *Proc Natl Acad Sci U S A.* 79(16):4848-52.

Chardin P., Camonis J.H., Gale N.W., van Aelst L., Schlessinger J., Wigler M.H., Bar-Sagi D. 1993 Human Sos1: a guanine nucleotide exchange factor for Ras that binds to GRB2. *Science* 260(5112):1338-43.

Chen R.H., Sarnecki C., Blenis J. 1992 Nuclear localization and regulation of erk- and rsk-encoded protein kinases. *Mol Cell Biol.* 12(3):915-27.

Chien Y., White M.A. 2003 RAL GTPases are linchpin modulators of human tumour-cell proliferation and survival. *EMBO Rep.* 4(8):800-6.

Choi K.M., McMahon L.P., Lawrence JC Jr. 2003 Two motifs in the translational repressor PHAS-I required for efficient phosphorylation by mammalian target of rapamycin and for recognition by raptor. *J Biol Chem.* 278(22):19667-73.

Christofk H.R., Vander Heiden M.G., Harris M.H., Ramanathan A., Gerszten R.E., Wei R., Fleming M.D., Schreiber S.L., Cantley L.C. 2008a The M2 splice isoform of pyruvate kinase is important for cancer metabolism and tumour growth. *Nature.* 452(7184):230-3.

Christofk H.R., Vander Heiden M.G., Wu N., Asara J.M., Cantley L.C. 2008b Pyruvate kinase M2 is a phosphotyrosine-binding protein. *Nature.* 452(7184):181-6.

Cloughesy T.F., Yoshimoto K., Nghiemphu P., Brown K., Dang J., Zhu S., Hsueh T., Chen Y., Wang W., Youngkin D., Liao L., Martin N., Becker D., Bergsneider M., Lai A., Green R., Oglesby T., Koleto M., Trent J., Horvath S., Mischel P.S., Mellinghoff I.K., Sawyers C.L. 2008 Antitumor activity of rapamycin in a Phase I trial for patients with recurrent PTEN-deficient glioblastoma. *PLoS Med.* 5(1):e8.

Coleman L.J., Peter M.B., Teall T.J., Brannan R.A., Hanby A.M., Honarpisheh H., Shaaban A.M., Smith L., Speirs V., Verghese E.T., McElwaine J.N., Hughes T.A.

2009 Combined analysis of eIF4E and 4E-binding protein expression predicts breast cancer survival and estimates eIF4E activity. *Br J Cancer*. 100(9):1393-9.

Coleman M.P., Rachet B., Woods L.M., Mityr E., Riga M., Cooper N., Quinn M.J., Brenner H., Estève J. 2004 Trends and socioeconomic inequalities in cancer survival in England and Wales up to 2001. *Br J Cancer*. 90(7):1367-73.

Contreras C.M., Gurumurthy S., Haynie J.M., Shirley L.J., Akbay E.A., Wingo S.N., Schorge J.O., Broaddus R.R., Wong K.K., Bardeesy N., Castrillon D.H. 2008 Loss of Lkb1 provokes highly invasive endometrial adenocarcinomas. *Cancer Res*. 68(3):759-66.

Cooper C.A., Carby F.A., Bubb V.J., Lamb D., Kerr K.M., Wyllie A.H. 1997 The pattern of K-ras mutation in pulmonary adenocarcinoma defines a new pathway of tumour development in the human lung. *J Pathol*. 181(4):401-4.

Crews C.M., Erikson R.L. 1992 Purification of a murine protein-tyrosine/threonine kinase that phosphorylates and activates the Erk-1 gene product: relationship to the fission yeast *byr1* gene product. *Proc Natl Acad Sci U S A*. 89(17):8205-9.

Crosas B., Hyndman D.J., Gallego O., Martras S., Parés X., Flynn T.G., Farrés J. 2003 Human aldose reductase and human small intestine aldose reductase are efficient retinal reductases: consequences for retinoid metabolism. *Biochem J*. 373(Pt 3):973-9

Darby S., Cross S.S., Brown N.J., Hamdy F.C., Robson C.N. 2008 BMP-6 over-expression in prostate cancer is associated with increased Id-1 protein and a more invasive phenotype. *J Pathol*. 214(3):394-404.

Davies H., Bignell G.R., Cox C., Stephens P., Edkins S., Clegg S., Teague J., Woffendin H., Garnett M.J., Bottomley W., Davis N., Dicks E., Ewing R., Floyd Y., Gray K., Hall S., Hawes R., Hughes J., Kosmidou V., Menzies A., Mould C., Parker A., Stevens C., Watt S., Hooper S., Wilson R., Jayatilake H., Gusterson B.A., Cooper C., Shipley J., Hargrave D., Pritchard-Jones K., Maitland N., Chenevix-Trench G., Riggins G.J., Bigner D.D., Palmieri G., Cossu A., Flanagan A., Nicholson A., Ho J.W., Leung S.Y., Yuen S.T., Weber B.L., Seigler H.F., Darrow T.L., Paterson H.,

Marais R., Marshall C.J., Wooster R., Stratton M.R., Futreal P.A. 2002 Mutations of the BRAF gene in human cancer. *Nature*. 417(6892):949-54.

Davies S.P., Sim A.T., Hardie D.G. 1990 Location and function of three sites phosphorylated on rat acetyl-CoA carboxylase by the AMP-activated protein kinase. *Eur J Biochem*. 187(1):183.

Decker T., Sandherr M., Goetze K., Oelsner M., Ringshausen I., Peschel C. 2009 A pilot trial of the mTOR (mammalian target of rapamycin) inhibitor RAD001 in patients with advanced B-CLL. *Ann Hematol*. 88(3):221-7.

DeFeo D., Gonda M.A., Young H.A., Chang E.H., Lowy D.R., Scolnick E.M., Ellis R.W. 1981 Analysis of two divergent rat genomic clones homologous to the transforming gene of Harvey murine sarcoma virus. *Proc Natl Acad Sci U S A*. 78(6):3328-32.

Ding L, Getz G, Wheeler DA, Mardis ER, McLellan MD, Cibulskis K, Sougnez C, Greulich H, Muzny DM, Morgan MB, Fulton L, Fulton RS, Zhang Q, Wendl MC, Lawrence MS, Larson DE, Chen K, Dooling DJ, Sabo A, Hawes AC, Shen H, Jhangiani SN, Lewis LR, Hall O, Zhu Y, Mathew T, Ren Y, Yao J, Scherer SE, Clerc K, Metcalf GA, Ng B, Milosavljevic A, Gonzalez-Garay ML, Osborne JR, Meyer R, Shi X, Tang Y, Koboldt DC, Lin L, Abbott R, Miner TL, Pohl C, Fewell G, Haippek C, Schmidt H, Dunford-Shore BH, Kraja A, Crosby SD, Sawyer CS, Vickery T, Sander S, Robinson J, Winckler W, Baldwin J, Chiriac LR, Dutt A, Fennell T, Hanna M, Johnson BE, Onofrio RC, Thomas RK, Tonon G, Weir BA, Zhao X, Ziaugra L, Zody MC, Giordano T, Orringer MB, Roth JA, Spitz MR, Wistuba II, Ozenberger B, Good PJ, Chang AC, Beer DG, Watson MA, Ladanyi M, Broderick S, Yoshizawa A, Travis WD, Pao W, Province MA, Weinstock GM, Varmus HE, Gabriel SB, Lander ES, Gibbs RA, Meyerson M, Wilson RK. 2008 Somatic mutations affect key pathways in lung adenocarcinoma. *Nature*. 455(7216):1069-75.

Dombrauckas J.D., Santarsiero B.D., Mesecar A.D. 2005 Structural basis for tumor pyruvate kinase M2 allosteric regulation and catalysis. *Biochemistry*. 44(27):9417-29.

Du P., Kibbe W.A., Lin S.M. 2008 lumi: a pipeline for processing Illumina Microarray. *Bioinformatics*. 24(13):1547-8.

Dudley D.T., Pang L., Decker S.J., Bridges A.J., Saltiel A.R. 1995 A synthetic inhibitor of the mitogen-activated protein kinase cascade. *Proc Natl Acad Sci U S A*. 92(17):7686-9.

Duncan R.F., Peterson H., Sevanian A. 2005 Signal transduction pathways leading to increased eIF4E phosphorylation caused by oxidative stress. *Free Radic Biol Med*. 38(5):631-43.

Dunlop E.A., Tee A.R. 2009 Mammalian target of rapamycin complex 1: signalling inputs, substrates and feedback mechanisms. *Cell Signal*. 21(6):827-35.

Edamatsu H., Satoh T., Kataoka T. 2006 Ras and Rap1 activation of PLCepsilon lipase activity. *Methods Enzymol*. 407:99-107.

Edkins S., O'Meara S., Parker A., Stevens C., Reis M., Jones S., Greenman C., Davies H., Dalgliesh G., Forbes S., Hunter C., Smith R., Stephens P., Goldstraw P., Nicholson A., Chan T.L., Velculescu V.E., Yuen S.T., Leung S.Y., Stratton M.R., Futreal P.A. 2006 Recurrent KRAS codon 146 mutations in human colorectal cancer. *Cancer Biol Ther*. Aug;5(8):928-32.

Eisen M.B., Spellman P.T., Brown P.O., Botstein D. 1998 Cluster analysis and display of genome-wide expression patterns. *Proc Natl Acad Sci U S A*. 95(25):14863-8.

Emuss V., Garnett M., Mason C., Marais R. 2005 Mutations of C-RAF are rare in human cancer because C-RAF has a low basal kinase activity compared with B-RAF. *Cancer Res*. 65(21):9719-26.

Entius M.M., Keller J.J., Westerman A.M., van Rees B.P., van Velthuysen M.L., de Goeij A.F., Wilson J.H., Giardiello F.M., Offerhaus G.J. 2001 Molecular genetic alterations in hamartomatous polyps and carcinomas of patients with Peutz-Jeghers syndrome. *J Clin Pathol*. 54(2):126-31.

Esteve-Puig R., Canals F., Colomé N., Merlino G., Recio J.A. 2009 Uncoupling of the LKB1-AMPKalpha energy sensor pathway by growth factors and oncogenic BRAF. *PLoS ONE*. 4(3):e4771.

Fantin V.R., St-Pierre J., Leder P. 2006 Attenuation of LDH-A expression uncovers a link between glycolysis, mitochondrial physiology, and tumor maintenance. *Cancer Cell*. 9(6):425-34.

Favata M.F., Horiuchi K.Y., Manos E.J., Daulerio A.J., Stradley D.A., Feeseer W.S., Van Dyk D.E., Pitts W.J., Earl R.A., Hobbs F., Copeland R.A., Magolda R.L., Scherle P.A., Trzaskos J.M. 1998 Identification of a novel inhibitor of mitogen-activated protein kinase kinase. *J Biol Chem*. 273(29):18623-32.

Fenton H., Carlile B., Montgomery E.A., Carraway H., Herman J., Sahin F., Su G.H., Argani P. 2006 LKB1 protein expression in human breast cancer. *Appl Immunohistochem Mol Morphol*. 14(2):146-53.

Ferlay J., Autier P, Boniol M., Heanue M., Colombet M., Boyle P. 2007 Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol*. 18(3):581-92.

Fernandes N., Sun Y., Chen S., Paul P., Shaw R.J., Cantley L.C., Price B.D. 2005 DNA damage-induced association of ATM with its target proteins requires a protein interaction domain in the N terminus of ATM. *J Biol Chem*. 280(15):15158-64

Fernandez P., Carretero J., Medina P.P., Jimenez A.I., Rodriguez-Perales S., Paz M.F., Cigudosa J.C., Esteller M., Lombardia L., Morente M., Sanchez-Verde L., Sotelo T., Sanchez-Cespedes M. 2004 Distinctive gene expression of human lung adenocarcinomas carrying LKB1 mutations. *Oncogene*. 23(29):5084-91.

Fingar D.C., Salama S., Tsou C., Harlow E., Blenis J. 2002 Mammalian cell size is controlled by mTOR and its downstream targets S6K1 and 4EBP1/eIF4E. *Genes Dev*. 16(12):1472-87.

Fingar D.C., Richardson C.J., Tee A.R., Cheatham L., Tsou C., Blenis J. 2004 mTOR controls cell cycle progression through its cell growth effectors S6K1 and 4EBP1/eukaryotic translation initiation factor 4E. *Mol Cell Biol*. 24(1):200-16.

Fisher T.L., Blenis J. 1996 Evidence for two catalytically active kinase domains in pp90rsk. *Mol Cell Biol*. 16(3):1212-9

Flaherty K., Puzanov I., Sosman J., Kim K., Ribas A., McArthur G., Lee R. J., Grippo J. F., Nolop K., Chapman P. 2009 Phase I study of PLX4032: Proof of concept for V600E BRAF mutation as a therapeutic target in human cancer *J Clin Oncol*. Vol 27: No 15S (May 20 Supplement)

Foretz M., Carling D., Guichard C., Ferré P., Foufelle F. 1998 AMP-activated protein kinase inhibits the glucose-activated expression of fatty acid synthase gene in rat hepatocytes. *J Biol Chem*. 273(24):14767-71.

Frias M.A., Thoreen C.C., Jaffe J.D., Schroder W., Sculley T., Carr S.A., Sabatini D.M. 2006 mSin1 is necessary for Akt/PKB phosphorylation, and its isoforms define three distinct mTORC2s. *Curr Biol*. 16(18):1865-70.

Fujimoto N., Wislez M., Zhang J., Iwanaga K., Dackor J., Hanna A.E., Kalyankrishna S., Cody D.D., Price R.E., Sato M., Shay J.W., Minna J.D., Peyton M., Tang X., Massarelli E., Herbst R., Threadgill D.W., Wistuba I.I., Kurie J.M. 2005 High expression of ErbB family members and their ligands in lung adenocarcinomas that are sensitive to inhibition of epidermal growth factor receptor. *Cancer Res*. 65(24):11478-85.

Fukumoto S., Yamauchi N., Moriguchi H., Hippo Y., Watanabe A., Shibahara J., Taniguchi H., Ishikawa S., Ito H., Yamamoto S., Iwanari H., Hironaka M., Ishikawa Y., Niki T., Sohara Y., Kodama T., Nishimura M., Fukayama M., Dosaka-Akita H., Aburatani H. Overexpression of the aldo-keto reductase family protein AKR1B10 is highly correlated with smokers' non-small cell lung carcinomas. 2005 *Clin Cancer Res*. 11(5):1776-85.

Futreal P.A., Coin L., Marshall M., Down T., Hubbard T., Wooster R., Rahman N., Stratton M.R. 2004 A census of human cancer genes. *Nat Rev Cancer*. 4(3):177-83.

Gallego O., Belyaeva O.V., Porté S., Ruiz F.X., Stetsenko A.V., Shabrova E.V., Kostereva N.V., Farrés J., Parés X., Kedishvili N.Y. 2006 Comparative functional analysis of human medium-chain dehydrogenases, short-chain dehydrogenases/reductases and aldo-keto reductases with retinoids. *Biochem J*. 399(1):101-9.

Gallego O., Ruiz F.X., Ardèvol A., Domínguez M., Alvarez R., de Lera A.R., Rovira C., Farrés J., Fita I., Parés X. 2007 Structural basis for the high all-trans-retinaldehyde reductase activity of the tumor marker AKR1B10. *Proc Natl Acad Sci U S A.* 104(52):20764-9.

Gambke C., Hall A., Moroni C. 1985 Activation of an N-ras gene in acute myeloblastic leukemia through somatic mutation in the first exon. *Proc Natl Acad Sci U S A.* 82(3):879-82.

Garami A., Zwartkruis F.J., Nobukuni T., Joaquin M., Rocco M., Stocker H., Kozma S.C., Hafen E., Bos J.L., Thomas G. 2003 Insulin activation of Rheb, a mediator of mTOR/S6K/4E-BP signaling, is inhibited by TSC1 and 2. *Mol Cell.* 11(6):1457-66.

García-Martínez J.M., Alessi D.R. 2008 mTOR complex 2 (mTORC2) controls hydrophobic motif phosphorylation and activation of serum- and glucocorticoid-induced protein kinase 1 (SGK1). *Biochem J.* 416(3):375-85.

Garnett M.J., Rana S., Paterson H., Barford D., Marais R. 2005 Wild-type and mutant B-RAF activate C-RAF through distinct mechanisms involving heterodimerization. *Mol Cell.* 20(6):963-9.

Gazzeri S., Brambilla E., Caron de Fromentel C., Gouyer V., Moro D., Perron P., Berger F., Brambilla C. 1994 p53 genetic abnormalities and myc activation in human lung carcinoma. *Int J Cancer.* 58(1):24-32.

Giardiello F.M., Brensinger J.D., Tersmette A.C., Goodman S.N., Petersen G.M., Booker S.V., Cruz-Correa M., Offerhaus J.A. 2000 Very high risk of cancer in familial Peutz-Jeghers syndrome. *Gastroenterology.* 119(6):1447-53.

Gimenez-Roqueplo A.P., Favier J., Rustin P., Mourad J.J., Plouin P.F., Corvol P., Rötig A., Jeunemaitre X. 2001 The R22X mutation of the SDHD gene in hereditary paraganglioma abolishes the enzymatic activity of complex II in the mitochondrial respiratory chain and activates the hypoxia pathway. *Am J Hum Genet.* 69(6):1186-97.

Gimenez-Roqueplo A.P., Favier J., Rustin P., Rieubland C., Kerlan V., Plouin P.F., Rötig A., Jeunemaitre X. 2002 Functional consequences of a SDHB gene mutation in an apparently sporadic pheochromocytoma. *J Clin Endocrinol Metab.* 87(10):4771-4.

Ginsberg R.J, Vokes E.E., Raben A. Section 2 non-small cell lung cancer. In chapter 30: Cancer of the lung. In: DeVita V.T., Jr., Hellman S., Rosenberg S.A., eds. *Cancer: principles and practice of oncology*, 5th ed. Philadelphia, PA: Lippincott-Raven, 1997;858–65.

Ginty D.D., Bonni A., Greenberg M.E. 1994 Nerve growth factor activates a Ras-dependent protein kinase that stimulates c-fos transcription via phosphorylation of CREB. *Cell.* 77(5):713-25.

Gordan J.D., Thompson C.B., Simon M.C. 2007 HIF and c-Myc: sibling rivals for control of cancer cell metabolism and proliferation. *Cancer Cell.* 12(2):108-13.

Graff J.R., Konicek B.W., Lynch R.L., Dumstorf C.A., Dowless M.S., McNulty A.M., Parsons S.H., Brail L.H., Colligan B.M., Koop J.W., Hurst B.M., Deddens J.A., Neubauer B.L., Stancato L.F., Carter H.W., Douglass L.E., Carter J.H. 2009 eIF4E activation is commonly elevated in advanced human prostate cancers and significantly related to reduced patient survival. *Cancer Res.* 69(9):3866-73.

Greer E.L., Oskoui P.R., Banko M.R., Maniar J.M., Gygi M.P., Gygi S.P., Brunet A. 2007a The energy sensor AMP-activated protein kinase directly regulates the mammalian FOXO3 transcription factor. *J Biol Chem.* 282(41):30107-19.

Greer E.L., Dowlatshahi D., Banko M.R., Villen J., Hoang K., Blanchard D., Gygi S.P., Brunet A. 2007b An AMPK-FOXO pathway mediates longevity induced by a novel method of dietary restriction in *C. elegans*. *Curr Biol.* 17(19):1646-56.

Grimshaw C.E., Bohren K.M., Lai C.J., Gabbay K.H. 1995 Human aldose reductase: rate constants for a mechanism including interconversion of ternary complexes by recombinant wild-type enzyme. *Biochemistry.* 34(44):14356-65.

Guertin D.A., Stevens D.M., Thoreen C.C., Burds A.A., Kalaany N.Y., Moffat J., Brown M., Fitzgerald K.J., Sabatini D.M. 2006 Ablation in mice of the mTORC

components raptor, rictor, or mLST8 reveals that mTORC2 is required for signaling to Akt-FOXO and PKC α , but not S6K1. *Dev Cell*. 11(6):859-71.

Hall A., Marshall C.J., Spurr N.K., Weiss R.A. 1983 Identification of transforming gene in two human sarcoma cell lines as a new member of the ras gene family located on chromosome 1. *Nature*. 303(5916):396-400.

Hao J., Daleo M.A., Murphy C.K., Yu P.B., Ho J.N., Hu J., Peterson R.T., Hatzopoulos A.K., Hong C.C. 2008 Dorsomorphin, a selective small molecule inhibitor of BMP signaling, promotes cardiomyogenesis in embryonic stem cells. *PLoS One*. 3(8):e2904

Han L., Colicelli J. 1995 A human protein selected for interference with Ras function interacts directly with Ras and competes with Raf1. *Mol Cell Biol*. 15(3):1318-23.

Han S.W., Kim T.Y., Jeon Y.K., Hwang P.G., Im S.A., Lee K.H., Kim J.H., Kim D.W., Heo D.S., Kim N.K., Chung D.H., Bang Y.J. 2006 Optimization of patient selection for gefitinib in non-small cell lung cancer by combined analysis of epidermal growth factor receptor mutation, K-ras mutation, and Akt phosphorylation. *Clin Cancer Res*. 12(8):2538-44.

Hanahan D., Weinberg R.A. 2000 The hallmarks of cancer. *Cell*. 100(1):57-70

Hara K., Yonezawa K., Kozlowski M.T., Sugimoto T., Andrabi K., Weng Q.P., Kasuga M., Nishimoto I., Avruch J. 1997 Regulation of eIF-4E BP1 phosphorylation by mTOR. *J Biol Chem*. 272(42):26457-63.

Hardie D.G., Carling D., Sim A.T. 1989 The AMP-activated protein kinase: a multisubstrate regulator of lipid metabolism. *Trends Biochem. Sci*. 14(1):20-23.

Hardie D.G., Salt I.P., Hawley S.A., Davies S.P. 1999 AMP-activated protein kinase: an ultrasensitive system for monitoring cellular energy charge. *Biochem J*. 338 (Pt 3):717-2.

Hawley S.A., Boudeau J., Reid J.L., Mustard K.J., Udd L., Mäkelä T.P., Alessi D.R., Hardie D.G. 2003 Complexes between the LKB1 tumor suppressor, STRAD

alpha/beta and MO25 alpha/beta are upstream kinases in the AMP-activated protein kinase cascade. *J Biol.* 2(4):28.

Hawley S.A., Pan D.A., Mustard K.J., Ross L., Bain J., Edelman A.M., Frenguelli B.G., Hardie D.G. 2005 Calmodulin-dependent protein kinase kinase-beta is an alternative upstream kinase for AMP-activated protein kinase. *Cell Metab.* 2(1):9-19

Heitman J., Movva N.R., Hall M.N. 1991 Targets for cell cycle arrest by the immunosuppressant rapamycin in yeast. *Science.* 253(5022):905-9.

Hemminki A., Tomlinson I., Markie D., Järvinen H., Sistonen P., Björkqvist A.M., Knuutila S., Salovaara R., Bodmer W., Shibata D., de la Chapelle A., Aaltonen L.A. 1997 Localization of a susceptibility locus for Peutz-Jeghers syndrome to 19p using comparative genomic hybridization and targeted linkage analysis. *Nat Genet.* 15(1):87-90.

Hemminki A., Markie D., Tomlinson I., Avizienyte E., Roth S., Loukola A., Bignell G., Warren W., Aminoff M., Höglund P., Järvinen H., Kristo P., Pelin K., Ridanpää M., Salovaara R., Toro T., Bodmer W., Olschwang S., Olsen AS., Stratton MR., de la Chapelle A., Aaltonen LA. 1998 A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. *Nature.* 391(6663):184-7

Hemminki A. 1999 The molecular basis and clinical aspects of Peutz-Jeghers syndrome. *Cell Mol Life Sci.* 55(5):735-50.

Henin N., Vincent M.F., Gruber H.E., Van den Berghe G. 1995 Inhibition of fatty acid and cholesterol synthesis by stimulation of AMP-activated protein kinase. *FASEB J.* 9(7):541-6.

Herbert T.P., Tee A.R., Proud C.G. 2002 The extracellular signal-regulated kinase pathway regulates the phosphorylation of 4E-BP1 at multiple sites. *J Biol Chem.* 277(13):11591-6.

Herrero-Martín G., Høyer-Hansen M., García-García C., Fumarola C., Farkas T., López-Rivas A., Jäättelä M. 2009 TAK1 activates AMPK-dependent cytoprotective autophagy in TRAIL-treated epithelial cells. *EMBO J.* 28(6):677-85.

Herzig S., Long F., Jhala U.S., Hedrick S., Quinn R., Bauer A., Rudolph D., Schutz G., Yoon C., Puigserver P., Spiegelman B., Montminy M. 2001 CREB regulates hepatic gluconeogenesis through the coactivator PGC-1. *Nature*. 413(6852):179-83.

Heyman R.A., Mangelsdorf D.J., Dyck J.A., Stein R.B., Eichele G., Evans R.M., Thaller C. 1992 9-cis retinoic acid is a high affinity ligand for the retinoid X receptor. *Cell*. 68(2):397-406.

Hezel A.F., Gurumurthy S., Granot Z., Swisa A., Chu G.C., Bailey G., Dor Y., Bardeesy N., Depinho R.A. 2008 Pancreatic LKB1 deletion leads to acinar polarity defects and cystic neoplasms. *Mol Cell Biol*. 28(7):2414-25.

Hirsch F.R., Varella-Garcia M., Bunn P.A. Jr., Di Maria M.V., Veve R., Bremmes R.M., Barón A.E., Zeng C., Franklin W.A. 2003 Epidermal growth factor receptor in non-small-cell lung carcinomas: correlation between gene copy number and protein expression and impact on prognosis. *J Clin Oncol*. 21(20):3798-807.

Hirsch F.R., Varella-Garcia M., Bunn P.A. Jr., Franklin W.A., Dziadziuszko R., Thatcher N., Chang A., Parikh P., Pereira J.R., Ciuleanu T., von Pawel J., Watkins C., Flannery A., Ellison G., Donald E., Knight L., Parums D., Botwood N., Holloway B. 2006 Molecular predictors of outcome with gefitinib in a phase III placebo-controlled study in advanced non-small-cell lung cancer. *J Clin Oncol*. 24(31):5034-42.

Hoffmann B., Leehmann J.M., Zhang, X.-K., Hermann T., Graupner G., Pfahl M. 1990 A retinoic acid receptor-specific element controls the retinoic acid receptor-b promoter. *Mol. Endocrinol.*, 4, 1734–1743.

Hofmann S.L. 1992 Retinoids--"differentiation agents" for cancer treatment and prevention. *Am J Med Sci*. 304(3):202-13.

Holness M.J., Kraus A., Harris R.A., Sugden M.C. 2000 Targeted upregulation of pyruvate dehydrogenase kinase (PDK)-4 in slow-twitch skeletal muscle underlies the stable modification of the regulatory characteristics of PDK induced by high-fat feeding. *Diabetes*. 49(5):775-81.

Houten S.M., Chegary M., Te Brinke H., Wijnen W.J., Glatz J.F., Luiken J.J., Wijburg F.A., Wanders R.J. 2009 Pyruvate dehydrogenase kinase 4 expression is

synergistically induced by AMP-activated protein kinase and fatty acids. *Cell Mol Life Sci.* 66(7):1283-94.

Huang B., Wu P., Bowker-Kinley M.M., Harris R.A. 2002 Regulation of pyruvate dehydrogenase kinase expression by peroxisome proliferator-activated receptor-alpha ligands, glucocorticoids, and insulin. *Diabetes.* 51(2):276-83.

Hundal R.S., Krssak M., Dufour S., Laurent D., Lebon V., Chandramouli V., Inzucchi S.E., Schumann W.C., Petersen K.F., Landau B.R., Shulman G.I. 2000 Mechanism by which metformin reduces glucose production in type 2 diabetes. *Diabetes.* 49(12):2063-9.

Huynh H., Ngo V.C., Koong H.N., Poon D., Choo S.P., Thng C.H., Chow P., Ong H.S., Chung A., Soo K.C. 2009 Sorafenib and Rapamycin Induce Growth Suppression in Mouse Models of Hepatocellular Carcinoma. *J Cell Mol Med.* Feb 9. [Epub ahead of print].

Hwang S.J., Cheng L.S., Lozano G., Amos C.I., Gu X., Strong L.C. 2003 Lung cancer risk in germline p53 mutation carriers: association between an inherited cancer predisposition, cigarette smoking, and cancer risk. *Hum Genet.* 113(3):238-43.

Iijima Y., Laser M., Shiraishi H., Willey C.D., Sundaravadivel B., Xu L., McDermott P.J., Kuppaswamy D. 2002 c-Raf/MEK/ERK pathway controls protein kinase C-mediated p70S6K activation in adult cardiac muscle cells. *J Biol Chem.* 277(25):23065-75.

Ikenoue T., Hikiba Y., Kanai F., Aragaki J., Tanaka Y., Imamura J., Imamura T., Ohta M., Ijichi H., Tateishi K., Kawakami T., Matsumura M., Kawabe T., Omata M. 2004 Different effects of point mutations within the B-Raf glycine-rich loop in colorectal tumors on mitogen-activated protein/extracellular signal-regulated kinase/extracellular signal-regulated kinase and nuclear factor kappaB pathway and cellular transformation. *Cancer Res.* 64(10):3428-35.

Ikenoue T., Kanai F., Hikiba Y., Tanaka Y., Imamura J., Ohta M., Jazag A., Guleng B., Asaoka Y., Tateishi K., Kawakami T., Matsumura M., Kawabe T., Omata M. 2005

Functional consequences of mutations in a putative Akt phosphorylation motif of B-raf in human cancers. *Mol Carcinog.* 43(1):59-63.

Im E., von Lintig F.C., Chen J., Zhuang S., Qui W., Chowdhury S., Worley P.F., Boss G.R., Pilz R.B. 2002 Rheb is in a high activation state and inhibits B-Raf kinase in mammalian cells. *Oncogene.* 21(41):6356-65.

Inoki K., Li Y., Zhu T., Wu J., Guan K.L. 2002 TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling. *Nat Cell Biol.* 9:648-57.

Irizarry R.A., Bolstad B.M., Collin .F, Cope L.M., Hobbs B., Speed T.P. 2003a Summaries of Affymetrix GeneChip probe level data. *Nucleic Acids Res.* 31(4):e15.

Irizarry R.A., Hobbs B., Collin F., Beazer-Barclay Y.D., Antonellis K.J., Scherf U., Speed T.P. 2003b Exploration, normalization, and summaries of high density oligonucleotide array probe level data. *Biostatistics.* 4(2):249-64.

Jacinto E., Loewith R., Schmidt A., Lin S., Rüegg M.A., Hall A., Hall M.N. 2004 Mammalian TOR complex 2 controls the actin cytoskeleton and is rapamycin insensitive. *Nat Cell Biol.* 6(11):1122-8.

Jacinto E., Facchinetti V., Liu D., Soto N., Wei S., Jung S.Y., Huang Q., Qin J., Su B. 2006 SIN1/MIP1 maintains rictor-mTOR complex integrity and regulates Akt phosphorylation and substrate specificity. *Cell.* 127(1):125-37.

Jackman D.M., Yeap B.Y., Lindeman N.I., Fidas P., Rabin M.S., Temel J., Skarin A.T., Meyerson M., Holmes A.J., Borrás A.M., Freidlin B., Ostler P.A., Lucca J., Lynch T.J., Johnson B.E., Jänne P.A. 2007 Phase II clinical trial of chemotherapy-naive patients ≥ 70 years of age treated with erlotinib for advanced non-small-cell lung cancer. *J Clin Oncol.* 25(7):760-6.

Jäger S., Handschin C., St-Pierre J., Spiegelman B.M. 2007 AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1 α . *Proc Natl Acad Sci U S A.* 104(29):12017-22.

Jaleel M., McBride A., Lizcano J.M., Deak M., Toth R., Morrice N.A., Alessi D.R. 2005 Identification of the sucrose non-fermenting related kinase SNRK, as a novel LKB1 substrate. *FEBS Lett.* 579(6):1417-23.

Janssen J.W., Steenvoorden A.C., Collard J.G., Nusse R. 1985 Oncogene activation in human myeloid leukemia. *Cancer Res.* 45(7):3262-7.

Jeghers H. 1944 Pigmentation of the skin. *N. Engl. J. Med.* 231:122-19.

Jeghers H., McKusick V.S., Katz K.H. 1949 Generalized intestinal polyposis and melanin spots of the oral mucosa, lips and digits. A syndrome of diagnostic significance. *N. Engl. J. Med.* 241:992-1005.

Jenne D.E., Reimann H., Nezu J., Friedel W., Loff S., Jeschke R., Müller O., Back W., Zimmer M. 1998 Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase. *Nat Genet.* 18(1):38-43.

Jez J.M., Flynn T.G., Penning T.M. 1997a A new nomenclature for the aldo-keto reductase superfamily. *Biochem Pharmacol.* 54(6):639-47.

Jez J.M., Bennett M.J., Schlegel B.P., Lewis M., Penning T.M. 1997b Comparative anatomy of the aldo-keto reductase superfamily. *Biochem J.* 326 (Pt 3):625-36.

Jez J.M., Penning T.M. 2001 The aldo-keto reductase (AKR) superfamily: an update. *Chem Biol Interact.* 130-132(1-3):499-525.

Ji H., Ramsey M.R., Hayes D.N., Fan C., McNamara K., Kozlowski P., Torrice C., Wu M.C., Shimamura T., Perera S.A., Liang M.C., Cai D., Naumov G.N., Bao L., Contreras C.M., Li D., Chen L., Krishnamurthy J., Koivunen J., Chirieac L.R., Padera R.F., Bronson R.T., Lindeman N.I., Christiani D.C., Lin X., Shapiro G.I., Jänne P.A., Johnson B.E., Meyerson M., Kwiatkowski D.J., Castrillon D.H., Bardeesy N., Sharpless N.E., Wong K.K. 2007 LKB1 modulates lung cancer differentiation and metastasis. *Nature.* 448(7155):807-10.

Jimenez A.I., Fernandez P., Dominguez O., Dopazo A., Sanchez-Cespedes M. 2003 Growth and molecular profile of lung cancer cells expressing ectopic LKB1: down-regulation of the phosphatidylinositol 3'-phosphate kinase/PTEN pathway. *Cancer Res.* 63(6):1382-8.

Jin Y., Penning T.M. 2007 Aldo-keto reductases and bioactivation/detoxication. *Annu Rev Pharmacol Toxicol.* 47:263-92.

Johnson L., Mercer K., Greenbaum D, Bronson R.T., Crowley D., Tuveson D.A., Jacks T. 2001 Somatic activation of the K-ras oncogene causes early onset lung cancer in mice. *Nature.* 410(6832):1111-6.

Jonas J.C., Sharma A., Hasenkamp W., Ilkova H., Patanè G., Laybutt R., Bonner-Weir S., Weir G.C. 1999 Chronic hyperglycemia triggers loss of pancreatic beta cell differentiation in an animal model of diabetes. *J Biol Chem.* 274(20):14112-21.

Jones S.W., Erikson E., Blenis J., Maller J.L., Erikson R.L. 1988 A *Xenopus* ribosomal protein S6 kinase has two apparent kinase domains that are each similar to distinct protein kinases. *Proc Natl Acad Sci U S A.* 85(10):3377-81.

Jones K.T., Greer E.R., Pearce D., Ashrafi K. 2009 Rictor/TORC2 regulates *Caenorhabditis elegans* fat storage, body size, and development through *sgk-1*. *PLoS Biol.* 7(3):e60.

Kahn B.B., Alquier T., Carling D., Hardie D.G. 2005 AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism. *Cell Metab.* 1(1):15-25

Karbowniczek M., Cash T., Cheung M., Robertson G.P., Astrinidis A., Henske E.P. 2004 Regulation of B-Raf kinase activity by tuberin and Rheb is mammalian target of rapamycin (mTOR)-independent. *J Biol Chem.* 279(29):29930-7.

Karbowniczek M., Robertson G.P., Henske E.P. 2006 Rheb inhibits C-raf activity and B-raf/C-raf heterodimerization. *J Biol Chem.* 281(35):25447-56.

Karuman P., Gozani O., Odze R.D., Zhou X.C., Zhu H., Shaw R., Brien T.P., Bozzuto C.D., Ooi D., Cantley L.C., Yuan J. 2001 The Peutz-Jegher gene product LKB1 is a mediator of p53-dependent cell death. *Mol Cell.* 7(6):1307-19.

Kemphues K.J., Priess J.R., Morton D.G., Cheng N.S. 1988 Identification of genes required for cytoplasmic localization in early *C. elegans* embryos. *Cell.* 52(3):311-20

Kim B., Lee H.J., Choi H.Y., Shin Y., Nam S., Seo G., Son D.S., Jo J., Kim J., Lee J., Kim J., Kim K., Lee S. 2007 Clinical validity of the lung cancer biomarkers identified by bioinformatics analysis of public expression data. *Cancer Res.* (15):7431-8.

Kim D.H., Sarbassov D.D., Ali S.M., King J.E., Latek R.R., Erdjument-Bromage H., Tempst P., Sabatini D.M. 2002 mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery. *Cell.* 110(2):163-75.

Kim D.H., Sarbassov D.D., Ali S.M., Latek R.R., Guntur K.V., Erdjument-Bromage H., Tempst P., Sabatini DM. 2003 GbetaL, a positive regulator of the rapamycin-sensitive pathway required for the nutrient-sensitive interaction between raptor and mTOR. *Mol Cell.* 11(4):895-904.

Kim C.F., Jackson E.L, Woolfenden A.E., Lawrence S., Babar I., Vogel S., Crowley D., Bronson R.T., Jacks T. 2005 Identification of bronchioalveolar stem cells in normal lung and lung cancer. *Cell.* 121(6):823-35

Kim Y.I., Lee F.N., Choi W.S., Lee S., Youn J.H. 2006 Insulin regulation of skeletal muscle PDK4 mRNA expression is impaired in acute insulin-resistant states. *Diabetes.* 55(8):2311-7.

Knauf U., Tschopp C., Gram H. 2001 Negative regulation of protein translation by mitogen-activated protein kinase-interacting kinases 1 and 2. *Mol Cell Biol.* 21(16):5500-11.

Koh H.J., Arnolds DE., Fujii N., Tran TT., Rogers M.J., Jessen N., Li Y., Liew C.W., Ho R.C., Hirshman M.F., Kulkarni R.N., Kahn C.R., Goodyear L.J. 2006 Skeletal muscle-selective knockout of LKB1 increases insulin sensitivity, improves glucose homeostasis, and decreases TRB3. *Mol Cell Biol.* 26(22):8217-27.

Koistinen H.A., Galuska D., Chibalin A.V., Yang J., Zierath J.R., Holman G.D., Wallberg-Henriksson H. 2003 5-amino-imidazole carboxamide riboside increases glucose transport and cell-surface GLUT4 content in skeletal muscle from subjects with type 2 diabetes. *Diabetes.* 52(5):1066-72.

Koivunen P., Hirsilä M., Remes A.M., Hassinen I.E., Kivirikko K.I., Myllyharju J. 2007 Inhibition of hypoxia-inducible factor (HIF) hydroxylases by citric acid cycle intermediates: possible links between cell metabolism and stabilization of HIF. *J Biol Chem.* 282(7):4524-32.

Kole H.K., Resnick R.J., Van Doren M., Racker E. 1991 Regulation of 6-phosphofructo-1-kinase activity in ras-transformed rat-1 fibroblasts. *Arch Biochem Biophys.* 286(2):586-90.

Koo S.H., Flechner L., Qi L., Zhang X., Srean R.A., Jeffries S., Hedrick S., Xu W., Boussouar F., Brindle P., Takemori H., Montminy M. 2005 The CREB coactivator TORC2 is a key regulator of fasting glucose metabolism. *Nature.* 437(7062):1109-11.

Kretschmar M., Doody J., Massagué J. 1997 Opposing BMP and EGF signalling pathways converge on the TGF-beta family mediator Smad1. *Nature.* 389(6651):618-22.

Kretschmar M., Doody J., Timokhina I., Massagué J. 1999 A mechanism of repression of TGFbeta/ Smad signaling by oncogenic Ras. *Genes Dev.* 13(7):804-16.

Kubota N., Terauchi Y., Kubota T., Kumagai H., Itoh S., Satoh H., Yano W., Ogata H., Tokuyama K., Takamoto .I, Mineyama T., Ishikawa M., Moroi M., Sugi K., Yamauchi T., Ueki K., Tobe K., Noda T., Nagai R., Kadowaki T. 2006 Pioglitazone ameliorates insulin resistance and diabetes by both adiponectin-dependent and -independent pathways. *J Biol Chem.* 281(13):8748-55.

Kuriyama M., Harada N., Kuroda S., Yamamoto T., Nakafuku M., Iwamatsu A., Yamamoto D., Prasad R., Croce C., Canaani E., Kaibuchi K. 1996 Identification of AF-6 and canoe as putative targets for Ras. *J Biol Chem.* 271(2):607-10.

Lambert J.M., Lambert Q.T., Reuther G.W., Malliri A., Siderovski D.P., Sondek J., Collard J.G., Der C.J. 2002 Tiam1 mediates Ras activation of Rac by a PI(3)K-independent mechanism. *Nat Cell Biol.* 4(8):621-5.

La Monica S., Galetti M., Alfieri R.R., Cavazzoni A., Ardizzoni A., Tiseo M., Capelletti M., Goldoni M., Tagliaferri S., Mutti A., Fumarola C., Bonelli M., Generali D.,

Petronini P.G. 2009 Everolimus restores gefitinib sensitivity in resistant non-small cell lung cancer cell lines. *Biochem Pharmacol.* 78(5):460-8.

LeBrasseur N.K., Kelly M., Tsao T.S., Farmer S.R., Saha A.K., Ruderman N.B., Tomas E. 2006 Thiazolidinediones can rapidly activate AMP-activated protein kinase in mammalian tissues. *Am J Physiol Endocrinol Metab.* 291(1):E175-81.

Liang X., Nan K.J., Li Z.L., Xu Q.Z. 2009 Overexpression of the LKB1 gene inhibits lung carcinoma cell proliferation partly through degradation of c-myc protein. *Oncol Rep.* 21(4):925-31.

Lin S.M., Du P., Kibbe W.A. 2008 Model-based Variance-stabilizing Transformation for Illumina Microarray Data. *Nucleic Acids Res.* 36(2):e11.

Lin T.A., Kong X., Saltiel A.R., Blakeshear P.J., Lawrence J.C. Jr. 1995 Control of PHAS-I by insulin in 3T3-L1 adipocytes. Synthesis, degradation, and phosphorylation by a rapamycin-sensitive and mitogen-activated protein kinase-independent pathway. *J Biol Chem.* 270(31):18531-8.

Lizcano J.M., Göransson O., Toth R., Deak M., Morrice N.A., Boudeau J., Hawley S.A., Udd L., Mäkelä T.P., Hardie D.G., Alessi D.R. 2004 LKB1 is a master kinase that activates 13 kinases of the AMPK subfamily, including MARK/PAR-1. *EMBO J.* 23(4):833-43.

Loewith R., Jacinto E., Wullschleger S., Lorberg A., Crespo J.L., Bonenfant D., Oppliger W., Jenoe P., Hall M.N. 2002 Two TOR complexes, only one of which is rapamycin sensitive, have distinct roles in cell growth control. *Mol Cell.* 10(3):457-68.

Long Y.C., Zierath J.R. 2006 AMP-activated protein kinase signaling in metabolic regulation. *J Clin Invest.* 116(7):1776-83.

Lorda-Diez C.I., Torre-Perez N., Garcia-Porrero J.A., Hurle J.M., Montero J.A. 2008 Expression of Id2 in the developing limb is associated with zones of active BMP signaling and marks the regions of growth and differentiation of the developing digits. *Int J Dev Biol.*

Lorusso P.M., Adjei A.A., Varterasian M., Gadgeel S., Reid J., Mitchell D.Y., Hanson L., DeLuca P., Bruzek L., Piens J., Asbury P., Van Becelaere K., Herrera R., Sebolt-Leopold J., Meyer M.B. 2005 Phase I and pharmacodynamic study of the oral MEK inhibitor CI-1040 in patients with advanced malignancies. *J Clin Oncol.* .23(23):5281-93.

Lotan R., (1981). Effect of vitamin A and its analogs (retinoids) on normal and neoplastic cells. *Biochim. Biophys. Acta.* 605, 33–91

Lotan R., Clifford J.L. 1991 Nuclear receptors for retinoids: mediators of retinoid effects on normal and malignant cells. *Biomed Pharmacother.*45(4-5):145-56.

Lowenstein E.J., Daly R.J., Batzer A.G., Li W., Margolis B., Lammers R., Ullrich A, Skolnik E.Y., Bar-Sagi D., Schlessinger J. 1992 The SH2 and SH3 domain-containing protein GRB2 links receptor tyrosine kinases to ras signaling. *Cell.* 70(3):431-42.

Lu C.W., Lin S.C., Chen K.F., Lai Y.Y., Tsai S.J. 2008 Induction of pyruvate dehydrogenase kinase-3 by hypoxia-inducible factor-1 promotes metabolic switch and drug resistance. *J Biol Chem.* 283(42):28106-14.

Luo Z., Saha AK., Xiang X., Ruderman N.B. 2005 AMPK, the metabolic syndrome and cancer. *Trends Pharmacol Sci.* 26(2):69-76.

Lynch T.J., Bell D.W., Sordella R., Gurubhagavatula S., Okimoto R.A., Brannigan B.W., Harris P.L., Haserlat S.M., Supko J.G., Haluska F.G., Louis D.N., Christiani D.C., Settleman J., Haber D.A. 2004 Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med.* 350(21):2129-39.

Ma J., Yan R., Zu X., Cheng J.M., Rao K., Liao D.F., Cao D. 2008 Aldo-keto reductase family 1 B10 affects fatty acid synthesis by regulating the stability of acetyl-CoA carboxylase- α in breast cancer cells. *J Biol Chem.* 283(6):3418-23.

Ma L., Chen Z., Erdjument-Bromage H., Tempst P., Pandolfi P.P. 2005 Phosphorylation and functional inactivation of TSC2 by Erk implications for tuberous sclerosis and cancer pathogenesis. *Cell.* 121(2):179-93

Ma L., Teruya-Feldstein J., Bonner P., Bernardi R., Franz D.N., Witte D., Cordon-Cardo C., Pandolfi P.P. 2007 Identification of S664 TSC2 phosphorylation as a marker for extracellular signal-regulated kinase mediated mTOR activation in tuberous sclerosis and human cancer. *Cancer Res.* 67(15):7106-12.

Ma X.M., Yoon S.O., Richardson C.J., Jülich K., Blenis J. 2008 SKAR links pre-mRNA splicing to mTOR/S6K1-mediated enhanced translation efficiency of spliced mRNAs. *Cell.* 133(2):303-13.

Macdonald J.S., McCoy S., Whitehead R.P., Iqbal S., Wade J.L. 3rd., Giguere J.K., Abbruzzese J.L. 2005 A phase II study of farnesyl transferase inhibitor R115777 in pancreatic cancer: a Southwest oncology group (SWOG 9924) study. *Invest New Drugs.* 23(5):485-7.

Macdonald S.G., Crews C.M., Wu L., Driller J., Clark R., Erikson R.L., McCormick F. 1993 Reconstitution of the Raf-1-MEK-ERK signal transduction pathway in vitro. *Mol Cell Biol.* 13(11):6615-20.

Mahoney C.L., Choudhury B., Davies H., Edkins S., Greenman C., Haafteen G., Mironenko T., Santarius T., Stevens C., Stratton M.R., Futreal P.A. 2009 LKB1/KRAS mutant lung cancers constitute a genetic subset of NSCLC with increased sensitivity to MAPK and mTOR signalling inhibition. *Br J Cancer.* 100(2):370-5.

Mallory SB, Stough DB 4th. 1987 Genodermatoses with malignant potential. *Dermatol Clin.* 5(1):221-30.

von Manteuffel S.R., Gingras A.C., Ming X.F., Sonenberg N., Thomas G. 1996 4E-BP1 phosphorylation is mediated by the FRAP-p70s6k pathway and is independent of mitogen-activated protein kinase. *Proc Natl Acad Sci U S A.* 93(9):4076-80.

Marais R, Wynne J, Treisman R. 1993 The SRF accessory protein Elk-1 contains a growth factor-regulated transcriptional activation domain. *Cell.* 73(2):381-93.

Marais R., Light Y., Paterson H.F., Mason C.S., Marshall C.J. 1997 Differential regulation of Raf-1, A-Raf, and B-Raf by oncogenic ras and tyrosine kinases. *J Biol Chem.* 272(7):4378-83.

Marby M., Nelkin B.D., Baylin S.B. Chapter 41 lung cancer. In: Vogelstein B, Kinzler KW, eds. 1998. The genetic basis of human cancer, 2nd edn. New York: The McGraw-Hill Companies, 671–9.

Martin S.G., St Johnston D. 2003 A role for Drosophila LKB1 in anterior-posterior axis formation and epithelial polarity. *Nature*. 421(6921):379-84.

Martin H.J., Breyer-Pfaff U., Wsol V., Venz S., Block S., Maser E. 2006 Purification and characterization of akr1b10 from human liver: role in carbonyl reduction of xenobiotics. *Drug Metab Dispos*. 34(3):464-70.

Martin H.J., Maser E. 2009 Role of human aldo-keto-reductase AKR1B10 in the protection against toxic aldehydes. *Chem Biol Interact*. 178(1-3):145-50.

Maruyama K., Watanabe H., Shiozaki H., Takayama T., Gofuku J., Yano H., Inoue M., Tamura S., Raz A., Monden M. 1995 Expression of autocrine motility factor receptor in human esophageal squamous cell carcinoma. *Int J Cancer*. 64(5):316-21.

Massarelli E., Varella-Garcia M., Tang X., Xavier A.C., Ozburn N.C., Liu D.D., Bekele B.N., Herbst R.S., Wistuba I.I. 2007 KRAS mutation is an important predictor of resistance to therapy with epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. *Clin Cancer Res*. 13(10):2890-6.

Matsumoto S., Iwakawa R., Takahashi K., Kohno T., Nakanishi Y., Matsuno Y., Suzuki K., Nakamoto M., Shimizu E., Minna J.D., Yokota J. 2007 Prevalence and specificity of LKB1 genetic alterations in lung cancers. *Oncogene*. 26(40):5911-8

Mazurek S., Boschek C.B., Hugo F., Eigenbrodt E. 2005 Pyruvate kinase type M2 and its role in tumor growth and spreading. *Semin Cancer Biol*. 15(4):300-8.

McGee S.L., Mustard K.J., Hardie D.G., Baar K. 2008 Normal hypertrophy accompanied by phosphorylation and activation of AMP-activated protein kinase alpha1 following overload in LKB1 knockout mice. *J Physiol*. 586(6):1731-41.

Mehenni H., Resta N., Park J.G., Miyaki M., Guanti G., Costanza M.C. 2006 Cancer risks in LKB1 germline mutation carriers. *Gut*. 55(7):984-90.

Mellanen P., Minn H., Grénman R., Härkönen P. 1994 Expression of glucose transporters in head-and-neck tumors. *Int J Cancer*. 56(5):622-9

Merrill G.F., Kurth E.J., Hardie D.G., Winder W.W. 1997 AICA riboside increases AMP-activated protein kinase, fatty acid oxidation, and glucose uptake in rat muscle. *Am J Physiol*. 273(6 Pt 1):E1107-12

Merrill GF, Kurth EJ, Rasmussen BB, Winder WW. 1998 Influence of malonyl-CoA and palmitate concentration on rate of palmitate oxidation in rat muscle. *J Appl Physiol*. 85(5):1909-14.

Milanini-Mongiati J., Pouysségur J., Pagès G. 2002 Identification of two Sp1 phosphorylation sites for p42/p44 mitogen-activated protein kinases: their implication in vascular endothelial growth factor gene transcription. *J Biol Chem*. 277(23):20631-9.

Miller V.A., Riely G.J., Zakowski M.F., Li A.R., Patel J.D., Heelan R.T., Kris M.G., Sandler A.B., Carbone D.P., Tsao A., Herbst R.S., Heller G., Ladanyi M., Pao W., Johnson D.H. 2008 Molecular characteristics of bronchioloalveolar carcinoma and adenocarcinoma, bronchioloalveolar carcinoma subtype, predict response to erlotinib. *J Clin Oncol*. 26(9):1472-8.

Milton D.T., Riely G.J., Azzoli C.G., Gomez J.E., Heelan R.T., Kris M.G., Krug L.M., Pao W., Pizzo B. Rizvi N.A., Miller V.A. 2007 Phase 1 trial of everolimus and gefitinib in patients with advanced nonsmall-cell lung cancer. *Cancer*. 110(3):599-605

Mirouse V., Swick L.L., Kazgan N., St Johnston D., Brenman J.E. 2007 LKB1 and AMPK maintain epithelial cell polarity under energetic stress. *J Cell Biol*. 177(3):387-92

Mirza A.M., Gysin S., Malek N., Nakayama K., Roberts J.M., McMahon M. 2004 Cooperative regulation of the cell division cycle by the protein kinases RAF and AKT. *Mol Cell Biol*. 24(24):10868-81.

Miyaki M., Iijima T., Hosono K., Ishii R., Yasuno M., Mori T., Toi M., Hishima T., Shitara N., Tamura K., Utsunomiya J., Kobayashi N., Kuroki T., Iwama T. 2000

Somatic mutations of LKB1 and beta-catenin genes in gastrointestinal polyps from patients with Peutz-Jeghers syndrome. *Cancer Res.* 60(22):6311-3.

Miyoshi H., Nakau M., Ishikawa T.O., Seldin M.F., Oshima M., Taketo M.M. 2002 Gastrointestinal hamartomatous polyposis in Lkb1 heterozygous knockout mice. *Cancer Res.* 62(8):2261-6.

Mountain C.F. 1997 Revisions in the International System for Staging Lung Cancer. *Chest.* 111(6):1710-7.

Monje P., Marinissen M.J., Gutkind J.S. 2003 Phosphorylation of the carboxyl-terminal transactivation domain of c-Fos by extracellular signal-regulated kinase mediates the transcriptional activation of AP-1 and cellular transformation induced by platelet-derived growth factor. *Mol Cell Biol.* 23(19):7030-43.

Momcilovic M., Hong S.P., Carlson M. 2006 Mammalian TAK1 activates Snf1 protein kinase in yeast and phosphorylates AMP-activated protein kinase in vitro. *J Biol Chem.* 281(35):25336-43.

Moodie S.A., Willumsen B.M., Weber M.J., Wolfman A. 1993 Complexes of Ras.GTP with Raf-1 and mitogen-activated protein kinase kinase. *Science.* 260(5114):1658-61.

Morton D.G., Roos J.M., Kempthues K.J. 1992 par-4, a gene required for cytoplasmic localization and determination of specific cell types in *Caenorhabditis elegans* embryogenesis. *Genetics.* 130(4):771-90.

Motzer R.J., Escudier B., Oudard S., Hutson T.E., Porta C., Bracarda S., Grünwald V., Thompson J.A., Figlin R.A., Hollaender N., Urbanowitz G., Berg W.J., Kay A., Lebwohl D., Ravaud A.; RECORD-1 Study Group 2008 Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet.* 372(9637):449-56.

Muoio D.M., MacLean P.S., Lang D.B., Li S., Houmard J.A., Way J.M., Winegar D.A., Corton J.C., Dohm G.L., Kraus W.E. 2002 Fatty acid homeostasis and induction of lipid regulatory genes in skeletal muscles of peroxisome proliferator-activated receptor (PPAR) alpha knock-out mice. Evidence for compensatory regulation by PPAR delta. *J Biol Chem.* 277(29):26089-97.

Murphy L.O., Blenis J. 2006 MAPK signal specificity: the right place at the right time. *Trends Biochem Sci.* 31(5):268-75.

Murray M.J., Cunningham J.M., Parada L.F., Dautry F., Lebowitz P., Weinberg R.A. 1983 The HL-60 transforming sequence: a ras oncogene coexisting with altered myc genes in hematopoietic tumors. *Cell.* 33(3):749-57.

Nakamori S., Watanabe H., Kameyama M., Imaoka S., Furukawa H., Ishikawa O., Sasaki Y., Kabuto T., Raz A. 1994 Expression of autocrine motility factor receptor in colorectal cancer as a predictor for disease recurrence. *Cancer.* 74(7):1855-62

Narbonne P., Roy R. 2006 Inhibition of germline proliferation during *C. elegans* dauer development requires PTEN, LKB1 and AMPK signalling. *Development.* 133(4):611-9.

Narbonne P., Roy R. 2009 *Caenorhabditis elegans* dauers need LKB1/AMPK to ration lipid reserves and ensure long-term survival. *Nature.* 457(7226):210-4.

Needleman S.W., Kraus M.H., Srivastava S.K., Levine P.H., Aaronson S.A. 1986 High frequency of N-ras activation in acute myelogenous leukemia. *Blood.* 67(3):75

Nezu J., Oku A., Shimane M. 1999 Loss of cytoplasmic retention ability of mutant LKB1 found in Peutz-Jeghers syndrome patients. *Biochem Biophys Res Commun.* 261(3):750-5.

Nicholson R.I., Gee J.M., Harper M.E. 2001 EGFR and cancer prognosis. *Eur J Cancer.* 37 Suppl 4:S9-15.

Niizeki H., Kobayashi M., Horiuchi I., Akakura N., Chen J., Wang J., Hamada J.I., Seth P., Katoh H., Watanabe H., Raz A., Hosokawa M. 2002 Hypoxia enhances the expression of autocrine motility factor and the motility of human pancreatic cancer cells. *Br J Cancer.* 86(12):1914-9.

Nojima H., Tokunaga C., Eguchi S., Oshiro N., Hidayat S., Yoshino K., Hara K., Tanaka N., Avruch J., Yonezawa K. 2003 The mammalian target of rapamycin (mTOR) partner, raptor, binds the mTOR substrates p70 S6 kinase and 4E-BP1 through their TOR signaling (TOS) motif. *J Biol Chem.* 278(18):15461-4.

Nowell P.C. 1976 The clonal evolution of tumor cell populations. *Science*. 194(4260):23-8.

Ohsaki Y., Tanno S., Fujita Y., Toyoshima E., Fujiuchi S., Nishigaki Y., Ishida S., Nagase A., Miyokawa N., Hirata S., Kikuchi K. 2000 Epidermal growth factor receptor expression correlates with poor prognosis in non-small cell lung cancer patients with p53 overexpression. *Oncol Rep*. 7(3):603-7.

Omenn G.S., Goodman G.E., Thornquist M.D., Balmes J., Cullen M.R., Glass A., Keogh J.P., Meyskens F.L., Valanis B., Williams J.H., Barnhart S., Hammar S.. 1996 Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med*. 334(18):1150-5.

Padua R.A., Barrass N.C., Currie G.A. 1985 Activation of N-ras in a human melanoma cell line. *Mol Cell Biol*. 5(3):582-5.

Paez J.G., Jänne P.A., Lee J.C., Tracy S., Greulich H., Gabriel S., Herman P., Kaye F.J., Lindeman N., Boggon T.J., Naoki K., Sasaki H., Fujii Y., Eck M.J., Sellers W.R., Johnson B.E., Meyerson M. 2004 EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. 304(5676):1497-500

Palozza P., Muzzalupo R., Trombino S., Valdannini A., Picci N. 2006 Solubilization and stabilization of beta-carotene in niosomes: delivery to cultured cells. *Chem Phys Lipids*. 139(1):32-42.

Pao W., Wang T.Y., Riely G.J., Miller V.A., Pan Q., Ladanyi M., Zakowski M.F., Heelan R.T., Kris M.G., Varmus H.E. 2005 KRAS mutations and primary resistance of lung adenocarcinomas to gefitinib or erlotinib. *PLoS Med*. 2(1):e17.

Parsons D.W., Jones S., Zhang X., Lin J.C., Leary R.J., Angenendt P., Mankoo P., Carter H., Siu I.M., Gallia G.L., Olivi A., McLendon R., Rasheed B.A., Keir S., Nikolskaya T., Nikolsky Y., Busam D.A., Tekleab H., Diaz L.A. Jr., Hartigan J., Smith D.R., Strausberg R.L., Marie S.K., Shinjo S.M., Yan H., Riggins G.J., Bigner D.D., Karchin R., Papadopoulos N., Parmigiani G., Vogelstein B., Velculescu V.E., Kinzler K.W. 2008 An integrated genomic analysis of human glioblastoma multiforme. *Science*. 321(5897):1807-12

Patel M.S., Roche T.E. 1990 Molecular biology and biochemistry of pyruvate dehydrogenase complexes. *FASEB J.* 4(14):3224-33.

Patel M.S., Korotchkina L.G. 2006 Regulation of the pyruvate dehydrogenase complex. *Biochem Soc Trans.* 34(Pt 2):217-22.

Pearce L.R., Huang X., Boudeau J., Pawłowski R., Wullschleger S., Deak M., Ibrahim A.F., Gourlay R., Magnuson M.A., Alessi D.R. 2007 Identification of Protor as a novel Rictor-binding component of mTOR complex-2. *Biochem J.* 405(3):513-22.

Penning T.M., Drury J.E. 2007 Human aldo-keto reductases: Function, gene regulation, and single nucleotide polymorphisms. *Arch Biochem Biophys.* 464(2):241-50.

Pérez-Gómez C., Campos-Sandoval J.A., Alonso F.J., Segura J.A., Manzanares E., Ruiz-Sánchez P., González M.E., Márquez J., Matés J.M. 2005 Co-expression of glutaminase K and L isoenzymes in human tumour cells. *Biochem J.* 386 (Pt 3):535-42.

Peutz J.L.A. 1921 Over een zeer merkwaardige gecombineerde familiale polyposis van de slijmvliezen, van den tractus intestinalis met die van de neuskeelholte en gepard met eigenaardige pigmentaties van huid en slijmvliezen. "Very remarkable case of familial polyposis of mucous membrane of intestinal tract and nasopharynx accompanied by peculiar pigmentation of skin and mucous membrane" *Ned. Maandschr Genesk.* 10:134-146.

Prowse C.N., Hagopian J.C., Cobb M.H., Ahn N.G., Lew J. 2000 Catalytic reaction pathway for the mitogen-activated protein kinase ERK2. *Biochemistry.* 39(20):6258-66.

Puigserver P., Spiegelman B.M. 2003 Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1 alpha): transcriptional coactivator and metabolic regulator. *Endocr Rev* 24(1):78-90.

Pullen N., Thomas G. 1997 The modular phosphorylation and activation of p70s6k. *FEBS Lett.* 410(1):78-82.

Qiu W., Schönleben F., Thaker H.M., Goggins M., Su G.H. 2006 A novel mutation of STK11/LKB1 gene leads to the loss of cell growth inhibition in head and neck squamous cell carcinoma. *Oncogene*. 25(20):2937-42.

Quinn M., Cooper N., Rowan S. 2005 Cancer Atlas of the United Kingdom and Ireland 1991-2000. Office for National Statistics.

Rapp U.R., Goldsborough M.D., Mark G.E., Bonner T.I., Groffen J., Reynolds F.H. Jr., Stephenson J.R. 1983 Structure and biological activity of v-raf, a unique oncogene transduced by a retrovirus. *Proc Natl Acad Sci U S A*. 80(14):4218-22.

Rappleye C.A., Tagawa A., Le Bot N., Ahringer J., Aroian R.V. 2003 Involvement of fatty acid pathways and cortical interaction of the pronuclear complex in *Caenorhabditis elegans* embryonic polarity. *BMC Dev Biol*. 3:8.

Raught B., Peiretti F., Gingras A.C., Livingstone M., Shahbazian D., Mayeur G.L., Polakiewicz R.D., Sonenberg N., Hershey J.W. 2004 Phosphorylation of eucaryotic translation initiation factor 4B Ser422 is modulated by S6 kinases. *EMBO J*. 23(8):1761-9.

Reddy E.P., Reynolds R.K., Santos E., Barbacid M. 1982 A point mutation is responsible for the acquisition of transforming properties by the T24 human bladder carcinoma oncogene. *Nature*. 300(5888):149-52.

Reynolds S.H., Anderson M.W. 1991 Activation of proto-oncogenes in human and mouse lung tumors. *Environ Health Perspect*. 93:145-8.

Reynolds S.H., Wiest J.S., Devereux T.R., Anderson M.W., You M. 1992 Protooncogene activation in spontaneously occurring and chemically induced rodent and human lung tumors. *Prog Clin Biol Res*. 376:303-20.

Richardson C.J., Bröenstrup M., Fingar D.C., Jülich K., Ballif B.A., Gygi S., Blenis J. 2004 SKAR is a specific target of S6 kinase 1 in cell growth control. *Curr Biol*. 14(17):1540-9.

Riely G.J., Kris M.G., Rosenbaum D., Marks J., Li A., Chitale D.A., Nafa K., Riedel E.R., Hsu M., Pao W., Miller V.A., Ladanyi M. 2008 Frequency and distinctive

spectrum of KRAS mutations in never smokers with lung adenocarcinoma. *Clin Cancer Res.* 14(18):5731-4.

Rinehart J., Adjei A.A., Lorusso P.M., Waterhouse D., Hecht J.R., Natale R.B., Hamid O., Varterasian M., Asbury P., Kaldjian E.P., Gulyas S., Mitchell D.Y., Herrera R., Sebolt-Leopold J.S., Meyer M.B. 2004 Multicenter phase II study of the oral MEK inhibitor, CI-1040, in patients with advanced non-small-cell lung, breast, colon, and pancreatic cancer. *J Clin Oncol.* 22(22):4456-62.

Roche T.E., Baker J.C., Yan X., Hiromasa Y., Gong X., Peng T., Dong J., Turkan A., Kasten S.A. 2001 Distinct regulatory properties of pyruvate dehydrogenase kinase and phosphatase isoforms. *Prog Nucleic Acid Res Mol Biol.* 70:33-75.

Roche T.E., Hiromasa Y. 2007 Pyruvate dehydrogenase kinase regulatory mechanisms and inhibition in treating diabetes, heart ischemia, and cancer. *Cell Mol Life Sci.* 64(7-8):830-49.

Rodriguez-Viciano P., Warne P.H., Dhand R., Vanhaesebroeck B., Gout I., Fry M.J., Waterfield M.D., Downward J. 1994 Phosphatidylinositol-3-OH kinase as a direct target of Ras. *Nature.* 370(6490):527-32.

Roelen B.A., Cohen O.S., Raychowdhury M.K., Chadee D.N., Zhang Y., Kyriakis J.M., Alessandrini A.A., Lin H.Y. 2003 Phosphorylation of threonine 276 in Smad4 is involved in transforming growth factor-beta-induced nuclear accumulation. *Am J Physiol Cell Physiol.* 285(4):C823-30.

Rosner M., Hanneder M., Siegel N., Valli A., Fuchs C., Hengstschläger M. 2008 The mTOR pathway and its role in human genetic diseases. *Mutat Res.* 659(3):284-92.

Rossomando A.J., Payne D.M., Weber M.J., Sturgill T.W. 1989 Evidence that pp42, a major tyrosine kinase target protein, is a mitogen-activated serine/threonine protein kinase. *Proc Natl Acad Sci U S A.* 86(18):6940-3.

Roux P.P., Ballif B.A., Anjum R., Gygi S.P., Blenis J. 2004 Tumor-promoting phorbol esters and activated Ras inactivate the tuberous sclerosis tumor suppressor complex via p90 ribosomal S6 kinase. *Proc Natl Acad Sci U S A.* 101(37):13489-94.

Roux P.P., Shahbazian D., Vu H., Holz M.K., Cohen M.S., Taunton J., Sonenberg N., Blenis J. 2007 RAS/ERK signaling promotes site-specific ribosomal protein S6 phosphorylation via RSK and stimulates cap-dependent translation. *J Biol Chem.* 282(19):14056-64

Ruderman N.B., Saha A.K., Vavvas D., Witters L.A. 1999 Malonyl-CoA, fuel sensing, and insulin resistance. *Am J Physiol.* 276(1 Pt 1):E1-E18.

Ruderman N.B., Park H., Kaushik V.K., Dean D., Constant S., Prentki M., Saha A.K. 2003 AMPK as a metabolic switch in rat muscle, liver and adipose tissue after exercise. *Acta Physiol Scand.* 178(4):435-42.

Ruiz FX., Gallego O., Ardèvol A., Moro A., Domínguez M., Alvarez S, Alvarez R., de Lera A.R., Rovira C., Fita I., Parés X., Farrés J. 2009 Aldo-keto reductases from the AKR1B subfamily: retinoid specificity and control of cellular retinoic acid levels. *Chem Biol Interact.* 178(1-3):171-7.

Rushworth L.K., Hindley A.D., O'Neill E., Kolch W. 2006 Regulation and role of Raf-1/B-Raf heterodimerization. *Mol Cell Biol.* 26(6):2262-72.

Sahin F., Maitra A., Argani P., Sato N., Maehara N., Montgomery E., Goggins M., Hruban R.H., Su G.H. 2003 Loss of Stk11/Lkb1 expression in pancreatic and biliary neoplasms. *Mod Pathol.* 16(7):686-91.

Sakamoto K., McCarthy A., Smith D., Green K.A., Grahame Hardie D., Ashworth A., Alessi D.R. 2005 Deficiency of LKB1 in skeletal muscle prevents AMPK activation and glucose uptake during contraction. *EMBO J.* 24(10):1810-20.

Sakamoto K., Zarrinpashneh E., Budas G.R., Pouleur A.C., Dutta A., Prescott A.R., Vanoverschelde J.L., Ashworth A., Jovanović A., Alessi D.R., Bertrand L. 2006 Deficiency of LKB1 in heart prevents ischemia-mediated activation of AMPKalpha2 but not AMPKalpha1. *Am J Physiol Endocrinol Metab.* 290(5):E780-8.

Saldanha A.J. 2004 Java Treeview--extensible visualization of microarray data. *Bioinformatics.* 20(17):3246-8.

Sanchez-Cespedes M., Parrella P., Esteller M., Nomoto S., Trink B., Engles J.M., Westra W.H., Herman J.G., Sidransky D. 2002 Inactivation of LKB1/STK11 is a common event in adenocarcinomas of the lung. *Cancer Res.* 62(13):3659-62.

Sanders M.J., Grondin P.O., Hegarty B.D., Snowden M.A., Carling D. 2007 Investigating the mechanism for AMP activation of the AMP-activated protein kinase cascade. *Biochem J.* 403(1):139-48.

Sapkota G.P., Kieloch A., Lizcano J.M., Lain S., Arthur J.S., Williams M.R., Morrice N., Deak M., Alessi D.R. 2001 Phosphorylation of the protein kinase mutated in Peutz-Jeghers cancer syndrome, LKB1/STK11, at Ser431 by p90(RSK) and cAMP-dependent protein kinase, but not its farnesylation at Cys(433), is essential for LKB1 to suppress cell growth. *J Biol Chem.* 276(22):19469-82.

Sapkota G.P., Boudeau J., Deak M., Kieloch A., Morrice N., Alessi D.R. 2002 Identification and characterization of four novel phosphorylation sites (Ser31, Ser325, Thr336 and Thr366) on LKB1/STK11, the protein kinase mutated in Peutz-Jeghers cancer syndrome. *Biochem J.* 362(Pt 2):481-90

Sarbassov D.D., Ali S.M., Kim D.H., Guertin D.A., Latek R.R., Erdjument-Bromage H., Tempst P., Sabatini D.M. 2004 Rictor, a novel binding partner of mTOR, defines a rapamycin-insensitive and raptor-independent pathway that regulates the cytoskeleton. *Curr Biol.* 14(14):1296-302.

Sato R., Goldstein J.L., Brown M.S. 1993 Replacement of serine-871 of hamster 3-hydroxy-3-methylglutaryl-CoA reductase prevents phosphorylation by AMP-activated kinase and blocks inhibition of sterol synthesis induced by ATP depletion. *Proc Natl Acad Sci U S A.* 90(20):9261-5.

Schalm S.S., Blenis J. 2002 Identification of a conserved motif required for mTOR signaling. *Curr Biol.* 12(8):632-9.

Scheper G.C., Morrice N.A., Kleijn M., Proud C.G. 2001 The mitogen-activated protein kinase signal-integrating kinase Mnk2 is a eukaryotic initiation factor 4E kinase with high levels of basal activity in mammalian cells. *Mol Cell Biol.* 21(3):743-54.

Sears R., Leone G., DeGregori J., Nevins J.R. 1999 Ras enhances Myc protein stability. *Mol Cell*. 3(2):169-79.

Sears R., Nuckolls F., Haura E., Taya Y., Tamai K., Nevins J.R. 2000 Multiple Ras-dependent phosphorylation pathways regulate Myc protein stability. *Genes Dev*. 14(19):2501-14.

Sebolt-Leopold J.S., Dudley D.T., Herrera R., Van Becelaere K., Wiland A., Gowan R.C., Teclé H, Barrett S.D, Bridges A., Przybranowski S., Leopold W.R., Saltiel A.R. 1999 Blockade of the MAP kinase pathway suppresses growth of colon tumors in vivo. *Nat Med*. 5(7):810-6.

Sebolt-Leopold J.S. 2008 Advances in the development of cancer therapeutics directed against the RAS-mitogen-activated protein kinase pathway. *Clin Cancer Res*. 14(12):3651-6.

Selak M.A., Armour S.M., MacKenzie E.D., Boulahbel H., Watson D.G., Mansfield K.D., Pan Y., Simon M.C., Thompson C.B., Gottlieb E. 2005 Succinate links TCA cycle dysfunction to oncogenesis by inhibiting HIF- α prolyl hydroxylase. *Cancer Cell*. 7(1):77-85.

Sewing A., Wiseman B., Lloyd A.C., Land H. 1997 High-intensity Raf signal causes cell cycle arrest mediated by p21Cip1. *Mol Cell Biol*. 17(9):5588-97.

Shahbazian D., Roux P.P., Mieulet V., Cohen M.S., Raught B., Taunton J., Hershey J.W., Blenis J., Pende M., Sonenberg N. 2006 The mTOR/PI3K and MAPK pathways converge on eIF4B to control its phosphorylation and activity. *EMBO J*. 25(12):2781-91.

Shaw R.J., Bardeesy N., Manning B.D., Lopez L., Kosmatka M., DePinho R.A., Cantley L.C. 2004a The LKB1 tumor suppressor negatively regulates mTOR signaling. *Cancer Cell*. 6(1):91-9.

Shaw R.J., Kosmatka M., Bardeesy N., Hurley R.L., Witters L.A., DePinho R.A., Cantley L.C. 2004b The tumor suppressor LKB1 kinase directly activates AMP-activated kinase and regulates apoptosis in response to energy stress. *Proc Natl Acad Sci U S A*. 101(10):3329-35.

Shaw R.J., Lamia K.A., Vasquez D., Koo S.H., Bardeesy N., Depinho R.A., Montminy M., Cantley L.C. 2005 The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. *Science*. 310(5754):1642-6.

Shen Z., Wen X.F., Lan F., Shen Z.Z., Shao Z.M. 2002 The tumor suppressor gene LKB1 is associated with prognosis in human breast carcinoma. *Clin Cancer Res*. 8(7):2085-90.

Shepherd T.G., Thériault B.L., Nachtigal M.W. 2008 Autocrine BMP4 signalling regulates ID3 proto-oncogene expression in human ovarian cancer cells. *Gene*. 414(1-2):95-105.

Shimamura A., Ballif B.A., Richards S.A., Blenis J. 2000 Rsk1 mediates a MEK-MAP kinase cell survival signal. *Curr Biol*. 10(3):127-35.

Shimizu K., Goldfarb M., Perucho M., Wigler M. 1983 Isolation and preliminary characterization of the transforming gene of a human neuroblastoma cell line. *Proc Natl Acad Sci U S A*. 80(2):383-7.

Smit V.T., Boot A.J., Smits A.M., Fleuren G.J., Cornelisse C.J., Bos J.L. 1988 KRAS codon 12 mutations occur very frequently in pancreatic adenocarcinomas. *Nucleic Acids Res*. 16(16):7773-82.

Smith D.P., Spicer J., Smith A., Swift S., Ashworth A. 1999 The mouse Peutz-Jeghers syndrome gene *Lkb1* encodes a nuclear protein kinase. *Hum Mol Genet*. 8(8):1479-85.

Smith C.M., Radzio-Andzelm E., Madhusudan., Akamine P., Taylor S.S. 1999 The catalytic subunit of cAMP-dependent protein kinase: prototype for an extended network of communication. *Prog Biophys Mol Biol*. 71(3-4):313-41.

Smyth G.K. 2004 Linear models and empirical bayes methods for assessing differential expression in microarray experiments. *Stat Appl Genet Mol Biol*. 3:Article3.

Soda M., Choi Y.L., Enomoto M., Takada S., Yamashita Y., Ishikawa S., Fujiwara S., Watanabe H., Kurashina K., Hatanaka H., Bando M., Ohno S., Ishikawa Y., Aburatani H., Niki T., Sohara Y., Sugiyama Y., Mano H. 2007 Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature*. 448(7153):561-6.

Solit D.B., Garraway L.A., Pratilas C.A., Sawai A., Getz G., Basso A., Ye Q., Lobo J.M., She Y., Osman I., Golub T.R., Sebolt-Leopold J., Sellers W.R., Rosen N. 2006 BRAF mutation predicts sensitivity to MEK inhibition. *Nature*. 439(7074):358-62.

Soria J.C., Shepherd F.A., Douillard J.Y., Wolf J., Giaccone G., Crino L., Cappuzzo F., Sharma S., Gross S.H., Dimitrijevic S., Di Scala L., Gardner H., Nogova L., Papadimitrakopoulou V. 2009 Efficacy of everolimus (RAD001) in patients with advanced NSCLC previously treated with chemotherapy alone or with chemotherapy and EGFR inhibitors. *Ann Oncol*. Jun 23. [Epub ahead of print].

Soukas A.A., Kane E.A., Carr C.E., Melo J.A., Ruvkun G. 2009 Rictor/TORC2 regulates fat metabolism, feeding, growth, and life span in *Caenorhabditis elegans*. *Genes Dev*. 23(4):496-511.

Strazisar M., Mlakar V., Rott T., Glavac D. 2009 Somatic alterations of the serine/threonine kinase LKB1 gene in squamous cell (SCC) and large cell (LCC) lung carcinoma. *Cancer Invest*. 27(4):407-16.

Su J.Y., Erikson E., Maller J.L. 1996 Cloning and characterization of a novel serine/threonine protein kinase expressed in early *Xenopus* embryos. *J Biol Chem*. 14;271(24):14430-7.

Su G.H., Hruban R.H., Bansal R.K., Bova G.S., Tang D.J., Shekher M.C., Westerman A.M., Entius M.M., Goggins M., Yeo C.J., Kern SE. 1999 Germline and somatic mutations of the STK11/LKB1 Peutz-Jeghers gene in pancreatic and biliary cancers. *Am J Pathol*. 154(6):1835-40.

Suwa M., Nakano H., Kumagai S. 2003 Effects of chronic AICAR treatment on fiber composition, enzyme activity, UCP3, and PGC-1 in rat muscles. *J Appl Physiol*. 95(3):960-8.

Tabin C.J., Bradley S.M., Bargmann C.I., Weinberg R.A., Papageorge A.G., Scolnick E.M., Dhar R., Lowy D.R., Chang E.H. 1982 Mechanism of activation of a human oncogene. *Nature*. 300(5888):143-9.

Takanami I., Takeuchi K., Naruke M., Kodaira S., Tanaka F., Watanabe H., Raz A. 1998 Autocrine motility factor in pulmonary adenocarcinomas: results of an immunohistochemical study. *Tumour Biol*. 19(5):384-9

Takeda S., Iwai A., Nakashima M., Fujikura D., Chiba S., Li H.M., Uehara J., Kawaguchi S., Kaya M., Nagoya S., Wada T., Yuan J., Rayter S., Ashworth A., Reed J.C., Yamashita T., Uede T., Miyazaki T. 2007 LKB1 is crucial for TRAIL-mediated apoptosis induction in osteosarcoma. *Anticancer Res*. 27(2):761-8.

Tan Y., Ruan H., Demeter M.R., Comb M.J. 1999 p90(RSK) blocks bad-mediated cell death via a protein kinase C-dependent pathway. *J Biol Chem*. Dec 3;274(49):34859-67.

Taparowsky E., Suard Y., Fasano O., Shimizu K., Goldfarb M., Wigler M. 1982 Activation of the T24 bladder carcinoma transforming gene is linked to a single amino acid change. *Nature*. 300(5894):762-5.

Taparowsky E., Shimizu K., Goldfarb M., Wigler M. 1983 Structure and activation of the human N-ras gene. *Cell*. 34(2):581-6.

Telang S., Yalcin A., Clem A.L., Bucala R., Lane A.N., Eaton J.W., Chesney J. 2006 Ras transformation requires metabolic control by 6-phosphofructo-2-kinase. *Oncogene*. 25(55):7225-34.

Tee A.R., Manning B.D., Roux P.P., Cantley L.C., Blenis J. 2003a Tuberous sclerosis complex gene products, Tuberin and Hamartin, control mTOR signaling by acting as a GTPase-activating protein complex toward Rheb. *Curr Biol*. 13(15):1259-68.

Tee A.R., Anjum R., Blenis J. 2003b Inactivation of the tuberous sclerosis complex-1 and -2 gene products occurs by phosphoinositide 3-kinase/Akt-dependent and -independent phosphorylation of tuberin. *J Biol Chem*. 278(39):37288-96.

Thomson D.M., Brown J.D., Fillmore N., Condon B.M., Kim H.J., Barrow J.R., Winder W.W. 2007 LKB1 and the regulation of malonyl-CoA and fatty acid oxidation in muscle. *Am J Physiol Endocrinol Metab.* 293(6):E1572-9.

Tiainen M., Ylikorkala A., Mäkelä T.P. 1999 Growth suppression by Lkb1 is mediated by a G(1) cell cycle arrest. *Proc Natl Acad Sci U S A.* 96(16):9248-51.

Tiainen M., Vaahtomeri K., Ylikorkala A., Mäkelä T.P. 2002 Growth arrest by the LKB1 tumor suppressor: induction of p21(WAF1/CIP1). *Hum Mol Genet.* 11(13):1497-504.

Tomlinson I.P., Houlston R.S. 1997 Peutz-Jeghers syndrome. *J Med Genet.* 34(12):1007-11.

Trumble G.E., Smith M.A., Winder W.W. 1995 Purification and characterization of rat skeletal muscle acetyl-CoA carboxylase. *Eur J Biochem.* 231(1):192-8.

Tsutsumi S., Yanagawa T., Shimura T., Kuwano H., Raz A. 2004 Autocrine motility factor signaling enhances pancreatic cancer metastasis. *Clin Cancer Res.* 10(22):7775-84.

Urano T., Emkey R., Feig L.A. 1996 Ral-GTPases mediate a distinct downstream signaling pathway from Ras that facilitates cellular transformation. *EMBO J.* 15(4):810-6.

Vander Heiden M.G., Cantley L.C., Thompson C.B. 2009 Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science.* (5930):1029-33

van't Veer L.J., Burgering B.M., Versteeg R., Boot A.J., Ruitter D.J., Osanto S., Schrier P.I., Bos J.L. 1989 N-ras mutations in human cutaneous melanoma from sun-exposed body sites. *Mol Cell Biol.* 9(7):3114-6.

Visvanathan K.V., Pockock R.D., Summerhayes I.C. 1988 Preferential and novel activation of H-ras in human bladder carcinomas. *Oncogene Res.* 3(1):77-86.

Vojtek A.B., Hollenberg S.M., Cooper J.A. 1993 Mammalian Ras interacts directly with the serine/threonine kinase Raf. *Cell.* 74(1):205-14.

Wan P.T., Garnett M.J., Roe S.M., Lee S., Niculescu-Duvaz D., Good V.M., Jones C.M., Marshall C.J., Springer C.J., Barford D., Marais R; Cancer Genome Project. 2004 Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. *Cell*. 116(6):855-67.

Wang D., Boerner S.A., Winkler J.D., LoRusso P.M.. Clinical experience of MEK inhibitors in cancer therapy. *Biochim Biophys Acta*. 2007 1773(8):1248-55.

Wang L., Gout I., Proud C.G. 2001 Cross-talk between the ERK and p70 S6 kinase (S6K) signaling pathways. MEK-dependent activation of S6K2 in cardiomyocytes. *J Biol Chem*. 276(35):32670-7.

Wang L., Harris T.E., Roth R.A., Lawrence J.C. Jr. 2007 PRAS40 regulates mTORC1 kinase activity by functioning as a direct inhibitor of substrate binding. *J Biol Chem*. 282(27):20036-44.

Wang S., Shi X. 2001 Mechanisms of Cr(VI)-induced p53 activation: the role of phosphorylation, mdm2 and ERK. *Carcinogenesis*. 22(5):757-62.

Wang X., Li W., Williams M., Terada N., Alessi D.R., Proud C.G. 2001 Regulation of elongation factor 2 kinase by p90(RSK1) and p70 S6 kinase. *EMBO J*. 20(16):4370-9.

Warburg O. On the origin of cancer cells. *Science*. 1956 Feb 24;123(3191):309-14.

Warne P.H., Viciano P.R., Downward J. 1993 Direct interaction of Ras and the amino-terminal region of Raf-1 in vitro. *Nature*. 364(6435):352-5.

Watson J.D., Crick F.H. 1953 Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. *Nature*. 171(4356):737-8.

Watts J.L., Morton D.G., Bestman J., Kempthues K.J. 2000 The *C. elegans* par-4 gene encodes a putative serine-threonine kinase required for establishing embryonic asymmetry. *Development*. 127(7):1467-75.

Westerman A.M, Wilson J.H. 1999 Peutz-Jeghers syndrome: risks of a hereditary condition. *Scand J Gastroenterol Suppl.* 230:64-70.

White M.A., Vale T., Camonis J.H., Schaefer E., Wigler M.H. 1996 A role for the Ral guanine nucleotide dissociation stimulator in mediating Ras-induced transformation. *J Biol Chem.* 271(28):16439-42.

Westra W.H., Slebos R.J., Offerhaus G.J., Goodman S.N., Evers S.G., Kensler T.W., Askin F.B., Rodenhuis S., Hruban R.H. 1993 K-ras oncogene activation in lung adenocarcinomas from former smokers. Evidence that K-ras mutations are an early and irreversible event in the development of adenocarcinoma of the lung. *Cancer.* 72(2):432-8.

Wilhelm S., Carter C., Lynch M., Lowinger T., Dumas J., Smith R.A., Schwartz B., Simantov R., Kelley S. 2006 Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. *Nat Rev Drug Discov.* 5(10):835-44.

Willumsen B.M., Christensen A., Hubbert N., Papageorge A.G., Lowy D.R. 1984 The p21 ras C-terminus is required for transformation and membrane association. *Nature.* 310(5978):583-6.

Winder W.W., Hardie D.G. 1996 Inactivation of acetyl-CoA carboxylase and activation of AMP-activated protein kinase in muscle during exercise. *Am J Physiol.* Feb;270(2 Pt 1):E299-304.

Winder W.W., Wilson H.A., Hardie D.G., Rasmussen B.B., Hutber C.A., Call G.B., Clayton R.D., Conley L.M., Yoon S., Zhou B. 1997 Phosphorylation of rat muscle acetyl-CoA carboxylase by AMP-activated protein kinase and protein kinase A. *J Appl Physiol.* 82(1):219-25.

Wingo S.N., Gallardo T.D., Akbay E.A., Liang M.C., Contreras C.M., Boren T., Shimamura T., Miller D.S., Sharpless N.E., Bardeesy N., Kwiatkowski D.J., Schorge J.O., Wong K.K., Castrillon D.H. 2009 Somatic LKB1 mutations promote cervical cancer progression. *PLoS ONE.* 4(4):e5137.

Wistuba I.I., Mao L., Gazdar A.F. 2002 Smoking molecular damage in bronchial epithelium. *Oncogene.* 21(48):7298-306.

Wolpin B.M., Hezel A.F., Abrams T., Blaszowsky L.S., Meyerhardt J.A., Chan J.A., Enzinger P.C., Allen B., Clark J.W., Ryan D.P., Fuchs C.S. 2009 Oral mTOR inhibitor everolimus in patients with gemcitabine-refractory metastatic pancreatic cancer. *J Clin Oncol.* 27(2):193-8.

Wong K.K. 2009 Recent developments in anti-cancer agents targeting the Ras/Raf/MEK/ERK pathway. *Recent Pat Anticancer Drug Discov.* 4(1):28-35.

Woods A., Azzout-Marniche D., Foretz M., Stein S.C., Lemarchand P., Ferré P., Foufelle F., Carling D. 2000 Characterization of the role of AMP-activated protein kinase in the regulation of glucose-activated gene expression using constitutively active and dominant negative forms of the kinase. *Mol Cell Biol.* 20(18):6704-11.

Woods A., Johnstone S.R., Dickerson K., Leiper F.C., Fryer L.G., Neumann D., Schlattner U., Wallimann T., Carlson M, Carling D. 2003 LKB1 is the upstream kinase in the AMP-activated protein kinase cascade. *Curr Biol.* 13(22):2004-8.

Woods D., Parry D., Cherwinski H., Bosch E., Lees E., McMahon M. 1997 Raf-induced proliferation or cell cycle arrest is determined by the level of Raf activity with arrest mediated by p21Cip1. *Mol Cell Biol.* 17(9):5598-611.

Wu P., Sato J., Zhao Y., Jaskiewicz J., Popov K.M., Harris R.A. 1998 Starvation and diabetes increase the amount of pyruvate dehydrogenase kinase isoenzyme 4 in rat heart. *Biochem J.* 329 (Pt 1):197-201.

Wu P., Inskeep K., Bowker-Kinley M.M., Popov K.M., Harris R.A. 1999 Mechanism responsible for inactivation of skeletal muscle pyruvate dehydrogenase complex in starvation and diabetes. *Diabetes.* 48(8):1593-9.

Wu P., Peters J.M., Harris R.A. 2001 Adaptive increase in pyruvate dehydrogenase kinase 4 during starvation is mediated by peroxisome proliferator-activated receptor alpha. *Biochem Biophys Res Commun.* 287(2):391-6.

Wu X., Noh S.J., Zhou G., Dixon J.E., Guan K.L. 1996 Selective activation of MEK1 but not MEK2 by A-Raf from epidermal growth factor-stimulated Hela cells. *J Biol Chem.* 271(6):3265-71.

Vos M.D., Ellis C.A., Elam C., Ulku A.S., Taylor B.J., Clark G.J. 2003 RASSF2 is a novel K-Ras-specific effector and potential tumor suppressor. *J Biol Chem.* 278(30):28045-51.

Xie M., Zhang D., Dyck J.R., Li Y., Zhang H., Morishima M., Mann D.L., Taffet G.E., Baldini A., Khoury D.S., Schneider M.D. 2006 A pivotal role for endogenous TGF-beta-activated kinase-1 in the LKB1/AMP-activated protein kinase energy-sensor pathway. *Proc Natl Acad Sci U S A.* 103(46):17378-83.

Xie Z., Dong Y., Zhang J., Scholz R., Neumann D., Zou M.H. 2009 Identification of the serine 307 of LKB1 as a novel phosphorylation site essential for its nucleocytoplasmic transport and endothelial cell angiogenesis. *Mol Cell Biol.* 29(13):3582-96.

Xing J., Ginty D.D., Greenberg M.E. 1996 Coupling of the RAS-MAPK pathway to gene activation by RSK2, a growth factor-regulated CREB kinase. *Science.* 273(5277):959-63.

Xu G.F., O'Connell P., Viskochil D., Cawthon R., Robertson M., Culver M., Dunn D., Stevens J., Gesteland R., White R. 1990 The neurofibromatosis type 1 gene encodes a protein related to GAP. *Cell.* 62(3):599-608.

Yan H., Parsons D.W., Jin G., McLendon R., Rasheed B.A., Yuan W., Kos I., Batinic-Haberle I., Jones S., Riggins G.J., Friedman H., Friedman A., Reardon D., Herndon J., Kinzler K.W., Velculescu V.E., Vogelstein B., Bigner D.D. 2009 IDH1 and IDH2 mutations in gliomas. *N Engl J Med.* 360(8):765-73.

Yanagawa T., Funasaka T., Tsutsumi S., Watanabe H., Raz A. 2004 Novel roles of the autocrine motility factor/phosphoglucose isomerase in tumor malignancy. *Endocr Relat Cancer.* 11(4):749-59.

Yang P., Ebbert J.O., Sun Z., Weinshilboum R.M. 2006 Role of the glutathione metabolic pathway in lung cancer treatment and prognosis: a review. *J Clin Oncol.* 24(11):1761-9.

Yan R., Zu X., Ma J., Liu Z., Adeyanju M., Cao D. 2007 Aldo-keto reductase family 1 B10 gene silencing results in growth inhibition of colorectal cancer cells: Implication for cancer intervention. *Int J Cancer.* 121(10):2301-6.

- Yang S.H., Yates P.R., Whitmarsh A.J., Davis R.J., Sharrocks A.D. 1998 The Elk-1 ETS-domain transcription factor contains a mitogen-activated protein kinase targeting motif. *Mol Cell Biol.* 18(2):710-20.
- Yang Q., Inoki K., Ikenoue T., Guan K.L. 2006 Identification of Sin1 as an essential TORC2 component required for complex formation and kinase activity. *Genes Dev.* 20(20):2820-32.
- Yoon J.C., Puigserver P., Chen G., Donovan J., Wu Z., Rhee J., Adelmant G., Stafford J., Kahn C.R., Granner D.K., Newgard C.B., Spiegelman B.M. 2001 Control of hepatic gluconeogenesis through the transcriptional coactivator PGC-1. *Nature.* 413(6852):131-8.
- Yoon S., Seger R. 2006 The extracellular signal-regulated kinase: multiple substrates regulate diverse cellular functions. *Growth Factors.* 24(1):21-44.
- Yu P.B., Hong C.C., Sachidanandan C., Babitt J.L., Deng D.Y., Hoyng S.A., Lin H.Y., Bloch K.D., Peterson R.T. 2008 Dorsomorphin inhibits BMP signals required for embryogenesis and iron metabolism. *Nat Chem Biol.* 4(1):33-41.
- Zhang X.K., Pfahl M. 1993 Hetero- and homodimeric receptors in thyroid hormone and vitamin A action. *Receptor.* 3(3):183-91.
- Zhang S., Schafer-Hales K., Khuri F.R., Zhou W., Vertino P.M., Marcus A.I. 2008 The tumor suppressor LKB1 regulates lung cancer cell polarity by mediating cdc42 recruitment and activity. *Cancer Res.* 68(3):740-8.
- Zhang X.F., Settleman J., Kyriakis J.M., Takeuchi-Suzuki E., Elledge S.J., Marshall M.S., Bruder J.T., Rapp U.R., Avruch J. 1993 Normal and oncogenic p21ras proteins bind to the amino-terminal regulatory domain of c-Raf-1. *Nature.* 364(6435):308-13.
- Zhang Y., Ma K., Sadana P., Chowdhury F., Gaillard S., Wang F., McDonnell D.P., Unterman T.G., Elam M.B., Park E.A. 2006 Estrogen-related receptors stimulate pyruvate dehydrogenase kinase isoform 4 gene expression. *J Biol Chem.* 281(52):39897-906.
- Zeqiraj E., Filippi B.M., Goldie S., Navratilova I., Boudeau J., Deak M., Alessi D.R., van Aalten D.M. 2009 ATP and MO25alpha regulate the conformational state of the

STRADalpha pseudokinase and activation of the LKB1 tumour suppressor. *PLoS Biol.* 7(6):e1000126.

Zeng P.Y., Berger S.L. 2006 LKB1 is recruited to the p21/WAF1 promoter by p53 to mediate transcriptional activation. *Cancer Res.* 66(22):10701-8

Zheng B., Jeong J.H., Asara J.M., Yuan Y.Y., Granter S.R., Chin L., Cantley L.C. 2009 Oncogenic B-RAF negatively regulates the tumor suppressor LKB1 to promote melanoma cell proliferation. *Mol Cell.* 33(2):237-47.

Zhong D., Guo L., de Aguirre I., Liu X., Lamb N., Sun S.Y., Gal A.A., Vertino P.M., Zhou W. 2006 LKB1 mutation in large cell carcinoma of the lung. *Lung Cancer.* 53(3):285-94.

Zhong D., Liu X., Khuri F.R., Sun S.Y., Vertino P.M., Zhou W. 2008 LKB1 is necessary for Akt-mediated phosphorylation of proapoptotic proteins. *Cancer Res.* 68(18):7270-7.

Zhong L., Liu Z., Yan R., Johnson S., Fang X., Cao D. 2009 Aldo-Keto Reductase Family 1 B10 Protein Detoxifies Dietary and Lipid-Derived Alpha, Beta-Unsaturated Carbonyls at Physiological Levels. *Biochem Biophys Res Commun.* Jun 26. Epub ahead of print.

Zhou G., Myers R., Li Y., Chen Y., Shen X., Fenyk-Melody J., Wu M., Ventre J., Doebber T., Fujii N., Musi N., Hirshman MF., Goodyear L.J., Moller D.E. 2001 Role of AMP-activated protein kinase in mechanism of metformin action. *J Clin Invest.* 108(8):1167-74.

Zhu C.Q., da Cunha Santos G., Ding K., Sakurada A., Cutz J.C., Liu N., Zhang T., Marrano P., Whitehead M., Squire J.A., Kamel-Reid S., Seymour L., Shepherd F.A., Tsao M.S; National Cancer Institute of Canada Clinical Trials Group Study BR.21. 2008 Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21. *J Clin Oncol.* 26(26):4268-75.

Zong H., Ren J.M., Young L.H., Pypaert M., Mu J., Birnbaum M.J., Shulman G.I.
2002 AMP kinase is required for mitochondrial biogenesis in skeletal muscle in
response to chronic energy deprivation. *Proc Natl Acad Sci U S A* 99(25):15983-7.