LECTURE #7: PROTEIN KINASES

Assigned (Required) Reading is (1) - (4):

(1) Johnson SA, Hunter T (2005) Kinomics: methods for deciphering the kinome. Nature Methods 2: 17-25.

(2) Bardwell L (2006) Mechanisms of MAPK signalling specificity. Biochem. Soc. Trans. 34: 837-841.

(3) Cowan-Jacob SW (2006) Structural biology of protein tyrosine kinases. Cell Mol Life Sci. 63: 2608-2625.

Paper for Friday Discussion Session (12/7):

Villa F, Goebel J, Rafiqi FH, Deak M, Thastrup J, Alessi DR, van Aalten DM (2007) Structural insights into the recognition of substrates and activators by the OSR1 kinase. EMBO Rep. 8: 839-845.

General Background:

Pellicena P, Kuriyan J (2006) Protein-protein interactions in the allosteric regulation of protein kinases. Curr Opin Struct Biol. 16: 702-709.

Pawson T, Scott JD (2005) Protein phosphorylation in signaling--50 years and counting. Trends Biochem. Sci. 30: 286-290.

Caenepeel S, Charydczak G, Sudarsanam S, Hunter T, Manning G. (2004) The mouse kinome: discovery and comparative genomics of all mouse protein kinases. Proc. Natl. Acad. Sci. USA 101: 11707-11712.

Manning G, Plowman GD, Hunter T, Sudarsanam S (2002) Evolution of protein kinase signaling from yeast to man. Trends Biochem. Sci. 27: 514-520.

Cohen P (2002) The origins of protein phosphorylation. Nature Cell Biol 4: E127-E130.

Huse M, Kuriyan J (2002) The conformational plasticity of protein kinases. Cell 109: 275-282.

Bingham J, Plowman GD, Sudarsanam S (2000) Informatics issues in large-scale sequence analysis: elucidating the protein kinases of C. elegans. J. Cell. Biochem. 80: 181-186.

Morrison DK, Murakami MS, Cleghon V (2000) Protein kinases and phosphatases in the Drosophila genome. J Cell Biol. 150: F57-F62.

Cohen P (2000) The regulation of protein function by multisite phosphorylation--a 25 year update. Trends Biochem Sci. 25: 596-601.

Johnson LN, Lowe ED, Noble ME, Owen DJ. (1998) The structural basis for substrate recognition and control by protein kinases (The Eleventh Datta Lecture). FEBS Lett. 430: 1-11.

Hunter, T. and G.D. Plowman (1997) The protein kinases of budding yeast: Six score and more. Trends Biochem. Sci. 22: 18-22.

Johnson LN, Noble ME, Owen DJ. (1996) Active and inactive protein kinases: structural basis for regulation. Cell 85: 149-158.

Selected examples of serine-, threonine-specific protein kinases:

Cyclic AMP-dependent protein kinase (PKA)—

Taylor SS, Yang J, Wu J, Haste NM, Radzio-Andzelm E, Anand G (2004) PKA: a portrait of protein kinase dynamics. Biochim. Biophys. A. 1697: 259-269.

Madhusudan, Akamine P, Xuong NH, Taylor SS (2002) Crystal structure of a transition state mimic of the catalytic subunit of cAMP-dependent protein kinase. Nature Struct. Biol. 9: 273-277.

Johnson DA, Akamine P, Radzio-Andzelm E, Madhusudan M, Taylor SS (2001) Dynamics of cAMP-dependent protein kinase. Chem. Rev. 101: 2243-2270.

Smith CM, Radzio-Andzelm E, Madhusudan KR, Akamine P, Taylor SS (1999) The catalytic subunit of cAMP-dependent protein kinase: prototype for an extended network of communication. Prog. Biophys. Mol. Biol. 71: 313-341.

McKnight GS, Cummings DE, Amieux PS, Sikorski MA, Brandon EP, Planas JV, Motamed K, Idzerda RL. (1998) Cyclic AMP, PKA, and physiological regulation. Recent Prog Horm Res. 53: 139-159.

Taylor SS, Zheng J, Radzio-Andzelm E, Knighton DR, Ten Eyck LF, Sowadski JM, Herberg FW, Yonemoto WM (1993) cAMP-dependent protein kinase defines a family of enzymes. Philos Trans R Soc Lond B Biol Sci. 340: 315-324.

Protein kinase C isotypes (PKC)—

Newton AC (2001) Protein kinase C: structural and spatial regulation by phosphorylation, cofactors, and macromolecular interactions. Chem Rev. 101: 2353-2364.

Dempsey EC, Newton AC, Mochly-Rosen D, Fields AP, Reyland ME, Insel PA, Messing RO (2000) Protein kinase C isozymes and the regulation of diverse cell responses. Am J Physiol Lung Cell Mol Physiol. 279: L429-L438.

Mellor H, Parker PJ (1998) The extended protein kinase C superfamily. Biochem J. 332: 281-292.

Other AGC family kinases—

Jaleel M, Villa F, Deak M, Toth R, Prescott AR, Van Aalten DM, Alessi DR. (2006) The ubiquitin-associated domain of AMPK-related kinases regulates conformation and LKB1-mediated phosphorylation and activation. Biochem J. 394: 545-555.

Tamaskovic R, Bichsel SJ, Hemmings BA (2003) NDR family of AGC kinases--essential regulators of the cell cycle and morphogenesis. FEBS Lett. 546: 73-80.

Dedicated and multifunctional Ca2+/calmodulin-dependent protein kinases—

Hudmon A, Schulman H (2002) Structure-function of the multifunctional Ca^{2+}/calmodulin-dependent protein kinase II. Biochem J. 364: 593-611.

Soderling TR, Chang B, Brickey D (2001) Cellular signaling through multifunctional Ca2+/calmodulin-dependent protein kinase II. J. Biol. Chem. 276: 3719-3722.

Heist EK, Schulman H (1998) The role of Ca^{2+}/calmodulin-dependent protein kinases within the nucleus. Cell Calcium 23: 103-114.

Stull JT, Kamm KE, Krueger JK, Lin P, Luby-Phelps K, Zhi G (1997) Ca2+/calmodulin-dependent myosin light-chain kinases. Adv Second Messenger Phosphoprotein Res. 31: 141-150.

c-Raf proto-oncogene product—

Mercer KE, Pritchard CA (2003) Raf proteins and cancer: B-Raf is identified as a mutational target. Biochim Biophys Acta 1653: 25-40

Kerkhoff E, Rapp UR (2001) The Ras-Raf relationship: an unfinished puzzle. Adv Enzyme Regul. 41: 261-267.

Morrison DK. (2001) KSR: a MAPK scaffold of the Ras pathway? J Cell Sci. 114: 1609-1612.

3-Phosphoinositide-dependent protein kinase, a "master" protein kinase—

Mora A, Komander D, van Aalten DM, Alessi DR (2004) PDK1, the master regulator of AGC kinase signal transduction. Semin. Cell Dev. Biol. 15: 161-170.

Brazil DP, Hemmings BA (2001) Ten years of protein kinase B signalling: a hard Akt to follow. Trends Biochem Sci. 26: 657-664.

Vanhaesebroeck B, Alessi DR. (2000) The PI3K-PDK1 connection: more than just a road to PKB. Biochem J. 346: 561-576.

Toker A, Newton AC (2000) Cellular signaling: pivoting around PDK-1. Cell 103: 185-188.

LKB1, another "master" kinase—

Alessi DR, Sakamoto K, Bayascas JR. (2006) Lkb1-dependent signaling pathways. Annu. Rev. Biochem. 75: 137-163.

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

Al-Hakim AK, Goransson O, Deak M, Toth R, Campbell DG, Morrice NA, Prescott AR, Alessi DR. (2005) 14-3-3 cooperates with LKB1 to regulate the activity and localization of QSK and SIK. J. Cell Sci. 118: 5661-5673.

Shaw RJ, Kosmatka M, Bardeesy N, Hurley RL, Witters LA, DePinho RA, Cantley LC (2004) The tumor suppressor LKB1 kinase directly activates AMP-activated kinase and regulates apoptosis in response to energy stress. Proc. Natl. Acad. Sci. USA 101: 3329-3335.

Spicer J, Ashworth A (2004) LKB1 kinase: master and commander of metabolism and polarity. Curr Biol. 14: R383-R385.

Carling D (2004) The AMP-activated protein kinase cascade--a unifying system for energy control. Trends Biochem Sci. 29: 18-24.

Green JB (2004) Lkb1 and GSK3-beta: kinases at the center and poles of the action. Cell Cycle 3: 12-14.

Boudeau J, Sapkota G, Alessi DR (2003) LKB1, a protein kinase regulating cell proliferation and polarity. FEBS Lett. 546: 159-165.

Hawley SA, Boudeau J, Reid JL, Mustard KJ, Udd L, Makela TP, Alessi DR, Hardie DG (2003) Complexes between the LKB1 tumor suppressor, STRADalpha/beta and MO25alpha/beta are upstream kinases in the AMP-activated protein kinase cascade. J Biol. 2: 28 [Epub 2003 Sep 24].

The Ste20/PAK family—

Buchwald G, Hostinova E, Rudolph MG, Kraemer A, Sickmann A, Meyer HE, Scheffzek K, Wittinghofer A (2001) Conformational switch and role of phosphorylation in PAK activation. Mol Cell Biol. 21: 5179-5189.

Lei M, Lu W, Meng W, Parrini MC, Eck MJ, Mayer BJ, Harrison SC (2000) Structure of PAK1 in an autoinhibited conformation reveals a multistage activation switch. Cell 102: 387-397.

Other Rac-, Rho- and Cdc42-activated protein kinases—

Amano M, Fukata Y, Kaibuchi K (2000) Regulation and functions of Rho-associated kinase. Exp Cell Res. 261: 44-51. Review.

Symons M, Settleman J (2000) Rho family GTPases: more than simple switches. Trends Cell Biol. 10: 415-419.

Mitogen- and stress-activated protein kinase cascades—

Raman M, Cobb MH (2003) MAP kinase modules: many roads home. Curr. Biol. 13: R886-R888.

Pouyssegur J, Volmat V, Lenormand P (2002) Fidelity and spatio-temporal control in MAP kinase (ERKs) signalling. Biochem Pharmacol. 64: 755-763.

Tanoue T, Nishida (2002) Docking interactions in the mitogen-activated protein kinase cascades. Pharmacol Ther. 93: 193-202.

Pearson G, Robinson F, Beers Gibson T, Xu BE, Karandikar M, Berman K, Cobb MH (2001) Mitogen-activated protein (MAP) kinase pathways: regulation and physiological functions. Endocr Rev. 22: 153-183.

Kyriakis JM, Avruch J (2001) Mammalian mitogen-activated protein kinase signal transduction pathways activated by stress and inflammation. Physiol Rev. 81: 807-869.

Garrington TP, Johnson GL. (1999) Organization and regulation of mitogen-activated protein kinase signaling pathways. Curr Opin Cell Biol 11: 211-218.

Miyata Y, Nishida E (1999) Distantly related cousins of MAP kinase: biochemical properties and possible physiological functions. Biochem Biophys Res Commun. 266: 291-295.

MAPK-activated protein kinases (including p90/RSK ribosomal protein S6 kinases)—

Roux PP, Blenis J (2004) ERK and p38 MAPK-activated protein kinases: a family of protein kinases with diverse biological functions. Microbiol Mol Biol Rev. 68: 320-344.

Meng W, Swenson LL, Fitzgibbon MJ, Hayakawa K, Ter Haar E, Behrens AE, Fulghum JR, Lippke JA (2002) Structure of mitogen-activated protein kinase-activated protein (MAPKAP) kinase-2 suggests a bifunctional switch that couples kinase activation with nuclear export. J. Biol. Chem. 277: 37401-37405.

Mahalingam M, Cooper JA (2001) Phosphorylation of mammalian eIF4E by Mnk1 and Mnk2: tantalizing prospects for a role in translation. Prog Mol Subcell Biol 27: 132-142.

Bhatt RR, Ferrell JE Jr. (2000) Cloning and characterization of Xenopus Rsk2, the predominant p90 Rsk isozyme in oocytes and eggs. J Biol Chem. 275(: 32983-32990.

Frodin M, Gammeltoft S. (1999) Roles and regulation of 90 kDa ribosomal S6 kinase (RSK) in signal transduction. Mol Cell Endocrinol. 151: 65-77.

Fukunaga R, Hunter T (1997) MNK1, a new MAP kinase-activated protein kinase, isolated by a novel expression screening method for identifying protein kinase substrates. EMBO J. 16: 1921-1933.

p70 and p85 ribosomal protein S6 kinases—

Volarevic S, Thomas G (2001) Role of S6 phosphorylation and S6 kinase in cell growth. Prog Nucleic Acid Res Mol Biol. 65: 101-127.

Stocker H, Hafen E (2000) Genetic control of cell size. Curr Opin Genet Dev. 10: 529-535.

Cdc5/Polo/Plk family—

Dai W, Huang X, Ruan Q (2003) Polo-like kinases in cell cycle checkpoint control. Front Biosci. 8: d1128-d1133.

Weitzer S, Uhlmann F (2002) Chromosome segregation: playing polo in prophase. Dev Cell. 2: 381-382.

Nigg EA (1998) Polo-like kinases: positive regulators of cell division from start to finish. Curr Opin Cell Biol. 10: 776-783.

Glover DM, Hagan IM, Tavares AA. (1998) Polo-like kinases: a team that plays throughout mitosis. Genes Dev. 12: 3777-3787.

Cyclin-dependent protein kinases—

Nurse P (2002) Cyclin dependent kinases and cell cycle control (Nobel lecture). Chembiochem. 3: 596-603.

Harper JW, Adams PD (2001) Cyclin-dependent kinases. Chem Rev. 101: 2511-2526.

Li A, Blow JJ (2001) The origin of CDK regulation. Nature Cell Biol. 3: E182-E184.

Morgan DO. (1997) Cyclin-dependent kinases: engines, clocks, and microprocessors. Annu Rev Cell Dev Biol. 13: 261-291.

Cdk-related protein kinases—

Tarricone C, Dhavan R, Peng J, Areces LB, Tsai LH, Musacchio A (2001) Structure and regulation of the CDK5-p25(nck5a) complex. Molecular Cell 8: 657-669.

Smith DS, Greer PL, Tsai LH (2001) Cdk5 on the brain. Cell Growth Differ. 12: 277-283.

Li BS, Sun M-K, Zhang L, Takahashi S, Ma W, Vinade L, Kulkarni AB, Brady RO, Pant HC (2001) Regulation of NMDA receptors by cyclin-dependent kinase-5. Proc. Natl. Acad. Sci. USA 98: 12742-12747.

<u>General Background (Protein-Tyrosine Kinases)</u>:

Blume-Jensen P, Hunter T (2001) Oncogenic kinase signalling. Nature 411: 355-365.

Hubbard SR, Till JH (2000) Protein tyrosine kinase structure and function. Annu. Rev. Biochem. 69: 373-398.

Robinson DR, Wu YM, Lin SF (2000) The protein tyrosine kinase family of the human genome. Oncogene 19: 5548-5557.

Schlessinger, J. (2000) Cell signaling by receptor tyrosine kinases. Cell 103: 211-226.

Hunter T. (1998) Croonian Lecture: the phosphorylation of proteins on tyrosine— its role in cell growth and disease. Philos Trans R Soc Lond B Biol Sci. 353: 583-605.

Sicheri, F. and J. Kuriyan (1997) Structures of Src-family tyrosine kinases. Current Opin. Structural Biol. 7: 777-785.

<u>Some Selected Examples</u>:

Src family kinases—

Courtneidge SA (2002) Role of SRC in signal transduction pathways. Biochem Soc Trans. 30: 11-17.

Martin GS (2001) The hunting of the Src. Nature Rev Mol Cell Biol. 2: 467-475.

Thomas SM, Brugge JS (1997) Cellular functions regulated by Src family kinases. Annu Rev Cell Dev Biol. 13: 513-609.

Focal adhesion zone kinase (FAK)—

Parsons JT, Martin KH, Slack JK, Taylor JM, Weed SA (2000) Focal adhesion kinase: a regulator of focal adhesion dynamics and cell movement. Oncogene 19: 5606-5613.

Rodriguez-Fernandez JL. (1999) Why do so many stimuli induce tyrosine phosphorylation of FAK? Bioessays 21: 1069-1075.

Syk—

Turner M, Schweighoffer E, Colucci F, Di Santo JP, Tybulewicz VL. (2000) Tyrosine kinase SYK: essential functions for immunoreceptor signalling. Immunol Today 21: 148-154.

Chu DH, Morita CT, Weiss A. (1998) The Syk family of protein tyrosine kinases in T-cell activation and development. Immunol Rev 165: 167-180.

Janus kinases (JAKs)—

Leonard WJ (2001) Role of Jak kinases and STATs in cytokine signal transduction. Int J Hematol. 73: 271-277.

Ihle JN. (1996) Janus kinases in cytokine signalling. Philos Trans R Soc Lond B Biol Sci. 351: 159-166.

c-Abl proto-oncogene product—

Shaul Y. (2000) c-Abl: activation and nuclear targets. Cell Death Differ. 7: 10-16.

Zou X, Calame K. (1999) Signaling pathways activated by oncogenic forms of Abl tyrosine kinase. J Biol Chem. 274: 18141-18144.

Tec family kinases—

Smith CI, Islam TC, Mattsson PT, Mohamed AJ, Nore BF, Vihinen M (2001) The Tec family of cytoplasmic tyrosine kinases: mammalian Btk, Bmx, Itk, Tec, Txk and homologs in other species. Bioessays 23: 436-446.

General Background (Dual-Specificity Kinases):

Taylor, S.S. , E. Radzio-Andzelm and T. Hunter (1995) How do protein kinases discriminate between serine/threonine and tyrosine? Structural insights from the insulin receptor protein-tyrosine kinase. FASEB Journal 9: 1255-1266.

Lindberg, R.A., A.M. Quinn and T. Hunter (1992) Dual-specificity protein kinases: will any hydroxyl do? Trends in Biochemical Sciences 17: 114-119.

MEKs (MAP kinase kinases)—

Ballif BA, Blenis J. (2001) Molecular mechanisms mediating mammalian mitogen-activated protein kinase (MAPK) kinase (MEK)-MAPK cell survival signals. Cell Growth Differ. 2001 Aug;12(8):397-408. Review. No abstract available.

Fukuda M, Gotoh I, Adachi M, Gotoh Y, Nishida E (1997) A novel regulatory mechanism in the mitogen-activated protein (MAP) kinase cascade. Role of nuclear export signal of MAP kinase kinase. J Biol Chem. 272: 32642-32648.

Wee1, Mik1 and Myt1—

Rhind N, Russell P (2001) Roles of the mitotic inhibitors Wee1 and Mik1 in the G(2) DNA damage and replication checkpoints. Mol Cell Biol. 21: 1499-1508.

Mueller PR, Coleman TR, Kumagai A, Dunphy WG. (1995) Myt1: a membrane-associated inhibitory kinase that phosphorylates Cdc2 on both threonine-14 and tyrosine-15. Science 270: 86-90.

Other examples—

Kassis S, Melhuish T, Annan RS, Chen SL, Lee JC, Livi GP, Creasy CL. (2000) *Saccharomyces cerevisiae* Yak1p protein kinase autophosphorylates on tyrosine residues and phosphorylates myelin basic protein on a C-terminal serine residue. Biochem J. 348: 263-272.

Duncan, P.I., B.W. Howell, R.M. Marius, S. Drmanic, E.M. Douville and J.C. Bell (1995) Alternative splicing of STY, a nuclear dual specificity kinase. J. Biol. Chem. 270: 21524-21531.

Lim MY, Dailey D, Martin GS, Thorner J. (1993) Yeast MCK1 protein kinase autophosphorylates at tyrosine and serine but phosphorylates exogenous substrates at serine and threonine. J Biol Chem. 268: 21155-21164.

Non-canonical protein kinases:

Richardson CJ, Schalm SS, Blenis J (2004) PI3-kinase and TOR: PIKTORing cell growth. Semin Cell Dev Biol. 15: 147-159.

Xu B, English JM, Wilsbacher JL, Stippec S, Goldsmith EJ, Cobb MH (2000) WNK1, a novel mammalian serine/threonine protein kinase lacking the catalytic lysine in subdomain II. J Biol Chem. 275: 16795-16801.

Schmelzle, T. and M.N. Hall (2000) TOR, a central controller of cell growth. Cell 103: 253-262.

Dedhar S. (2000) Cell-substrate interactions and signaling through ILK. Curr Opin Cell Biol. 12: 250-256.

Rotman G, Shiloh Y. (1999) ATM: a mediator of multiple responses to genotoxic stress. Oncogene 18: 6135-6144.

Smith GC, Jackson SP. (1999) The DNA-dependent protein kinase. Genes Dev. 13: 916-934.

Practical Matters:

Cohen MS, Zhang C, Shokat KM, Taunton J. (2005) Structural bioinformatics-based design of selective, irreversible kinase inhibitors. Science 308: 1318-1321.

Knight ZA, Schilling B, Row RH, Kenski DM, Gibson BW, Shokat KM. (2003) Phosphospecific proteolysis for mapping sites of protein phosphorylation. Nature Biotechnol. 21: 1047-1054'; Erratum 21: 1396.

Shou W, Verma R, Annan RS, Huddleston MJ, Chen SL, Carr SA, Deshaies RJ (2002) Mapping phosphorylation sites in proteins by mass spectrometry. Methods Enzymol. 351: 279-296.

Mann M, Ong SE, Gronborg M, Steen H, Jensen ON, Pandey A (2002) Analysis of protein phosphorylation using mass spectrometry: deciphering the phosphoproteome. Trends Biotechnol. 20: 261-268.

Conrads TP, Issaq HJ, Veenstra TD (2002) New tools for quantitative phosphoproteome analysis. Biochem Biophys Res Commun 290: 885-890.

Songyang Z (2001) Analysis of protein kinase specificity by peptide libraries and prediction of in vivo substrates. Methods Enzymol. 332: 171-183.

Bishop AC, Buzko O, Shokat KM (2001) Magic bullets for protein kinases. Trends Cell Biol. 11: 167-172.

McLachlin DT, Chait BT (2001) Analysis of phosphorylated proteins and peptides by mass spectrometry. Curr Opin Chem Biol. 5: 591-602.

Zhou H, Watts JD, Aebersold R (2001) A systematic approach to the analysis of protein phosphorylation. Nature Biotechnol. 19: 375-378.

Bishop AC, Ubersax JA, Petsch DT, Matheos DP, Gray NS, Blethrow J, Shimizu E, Tsien JZ, Schultz PG, Rose MD, Wood JL, Morgan DO, Shokat KM (2000) A chemical switch for inhibitor-sensitive alleles of any protein kinase. Nature 407: 395-401.

Cuenda A, Alessi DR (2000) Use of kinase inhibitors to dissect signaling pathways. Methods Mol Biol. 99: 161-175.

Oda Y, Huang K, Cross FR, Cowburn D, Chait BT (1999) Accurate quantitation of protein expression and site-specific phosphorylation. Proc Natl Acad Sci U S A 96: 6591-6596.

Gray NS; Wodicka L; Thunnissen AM; Norman TC; Kwon S; Espinoza FH; Morgan DO; Barnes G; LeClerc S; Meijer L; et al. (Schultz, P.G.) (1998) Exploiting chemical libraries, structure, and genomics in the search for kinase inhibitors. Science 281: 533-538.

Eukaryotic-like protein kinases in bacteria:

Greenstein AE, Grundner C, Echols N, Gay LM, Lombana TN, Miecskowski CA, Pullen KE, Sung PY, Alber T (2005) Structure/function studies of Ser/Thr and Tyr protein phosphorylation in *Mycobacterium tuberculosis*. J Mol Microbiol Biotechnol. 9: 167-181.

Kennelly PJ. (2003) Archaeal protein kinases and protein phosphatases: insights from genomics and biochemistry. Biochem. J. 370: 373-389.

Petrickova K, Petricek M. (2003) Eukaryotic-type protein kinases in *Streptomyces coelicolor*: variations on a common theme. Microbiology 149: 1609-1621.

Av-Gay Y, Everett M. (2000) The eukaryotic-like Ser/Thr protein kinases of *Mycobacterium tuberculosis*. Trends Microbiol. 8: 238-244.

Zhang CC. (1996) Bacterial signalling involving eukaryotic-type protein kinases. Mol. Microbiol. 20: 9-15.