

LECTURE #10: REGULATION OF CELL PROLIFERATION AND CELL SURVIVAL

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

•General Background (in your Reader):

- (1) Hanahan D, Weinberg RA (2000) The hallmarks of cancer. *Cell* 100: 57-70.
- (2) Sherr CJ (2004) Principles of tumor suppression. *Cell* 116: 235-246.
- (3) Adams JM, Cory S (2007) Bcl-2-regulated apoptosis: mechanism and therapeutic potential. *Curr. Opin. Immunol.* 19: 488-496.

•Paper for Discussion Session (Mon., 17 Dec.):

- (4) Dai C, Whitesell L, Rogers AB, Lindquist S (2007) Heat shock factor 1 is a powerful multifaceted modifier of carcinogenesis. *Cell* 130: 1005-1018.

The Cell Cycle (general background):

Morgan DO (2007) *The Cell Cycle: Principles of Control*, New Science Press, Ltd., London, UK, 297pp.

Massague J (2004) G1 cell-cycle control and cancer. *Nature* 432: 298-306.

Pines J, Rieder CL (2001) Re-staging mitosis: a contemporary view of mitotic progression. *Nature Cell Biol.* 3: E3-E6.

Nurse P (2000) A long twentieth century of the cell cycle and beyond. *Cell.* 100: 71-78.

Cook SJ, Balmanno K, Garner A, Millar T, Taverner C, Todd D. (2000) Regulation of cell cycle re-entry by growth, survival and stress signalling pathways. *Biochem Soc Trans.* 28: 233-240.

Murray, A and T. Hunt (1993) *The cell cycle: an introduction*. W.H Freeman & Co., New York, NY, 251pp.

Cyclin-Dependent Protein Kinases (CDKs):

Santamaria D, Ortega S (2006) Cyclins and CDKS in development and cancer: lessons from genetically modified mice. *Front. Biosci.* 11: 1164-1188.

Gray CH, Barford D. (2003) Getting in the ring: proline-directed substrate specificity in the cell cycle proteins Cdc14 and CDK2-cyclinA3. *Cell Cycle* 2: 500-502.

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.

Gitig DM, Koff A. (2000) Cdk pathway: cyclin-dependent kinases and cyclin-dependent kinase inhibitors. *Methods Mol Biol.* 142: 109-123.

Ekholm SV, Reed SI (2000) Regulation of G(1) cyclin-dependent kinases in the mammalian cell cycle. *Curr Opin Cell Biol.* 12: 676-684.

Malumbres M, Ortega S, Barbacid M. (2000) Genetic analysis of mammalian cyclin-dependent kinases and their inhibitors. *Biol Chem.* 381: 827-838.

Moffat J, Huang D, Andrews B. (2000) Functions of Pho85 cyclin-dependent kinases in budding yeast. *Prog Cell Cycle Res.* 4: 97-106.

Takizawa CG, Morgan DO (2000) Control of mitosis by changes in the subcellular location of cyclin-B1-Cdk1 and Cdc25C. *Curr Opin Cell Biol.* 12: 658-665.

Pavletich NP (1999) Mechanisms of cyclin-dependent kinase regulation: structures of Cdk, their cyclin activators, and Cip and INK4 inhibitors. *J Mol Biol.* 287: 821-828.

Endicott JA, Noble ME, Tucker JA. (1999) Cyclin-dependent kinases: inhibition and substrate recognition. *Curr Opin Struct Biol.* 9: 738-744.

Johnston LH, Masai H, Sugino A. (1999) First the CDKs, now the DDKs. *Trends Cell Biol.* 9: 249-252.

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

Cyclins:

Sherr CJ, Roberts JM. (2004) Living with or without cyclins and cyclin-dependent kinases. *Genes Dev.* 18: 2699-2711.

Miller ME, Cross FR (2001) Cyclin specificity: how many wheels do you need on a unicycle? *J Cell Sci.* 114: 1811-1820.

Laman H, Mann DJ, Jones NC (2000) Virally-encoded cyclins. *Curr Opin Genet Dev.* 10: 70-74.

Roberts JM (1999) Evolving ideas about cyclins. *Cell.* 98: 129-132.

Yang J, Kornbluth S (1999) All aboard the cyclin train: subcellular trafficking of cyclins and their CDK partners. *Trends Cell Biol.* 9: 207-210.

Suc1/Cks:

Harper JW (2001) Protein destruction: adapting roles for Cks proteins. *Curr Biol.* 11: R431-R435.

Ganoth D, Bornstein G, Ko TK, Larsen B, Tyers M, Pagano M, Hershko A (2001) The cell-cycle regulatory protein Cks1 is required for SCF(Skp2)-mediated ubiquitinylation of p27. *Nature Cell Biol.* 3: 321-324.

Spruck C, Strohmaier H, Watson M, Smith AP, Ryan A, Krek TW, Reed SI. (2001) A CDK-independent function of mammalian Cks1: targeting of SCF(Skp2) to the CDK inhibitor p27Kip1. *Mol Cell.* 7: 639-650.

Landrieu I, Odaert B, Wieruszkeski JM, Drobecq H, Rousselot-Pailley P, Inze D, Lippens G (2001) p13(SUC1) and the WW domain of PIN1 bind to the same phosphothreonine-proline epitope. *J Biol Chem.* 276: 1434-1438.

Reynard GJ, Reynolds W, Verma R, Deshaies RJ. (2000) Cks1 is required for G(1) cyclin-cyclin-dependent kinase activity in budding yeast. *Mol Cell Biol.* 20: 5858-5864.

Control of G2/M Progression (entry and exit from mitosis):

Jensen S, Johnston LH (2002) Complexity of mitotic exit. *Cell Cycle* 1: 300-303.

Irniger S (2002) Cyclin destruction in mitosis: a crucial task of Cdc20. *FEBS Lett.* 532: 7-11

Surana U, Yeong FM, Lim HH (2002) MEN, destruction and separation: mechanistic links between mitotic exit and cytokinesis in budding yeast. *Bioessays* 24: 659-666.

Cid VJ, Jimenez J, Molina M, Sanchez M, Nombela C, Thorner JW (2002) Orchestrating the cell cycle in yeast: sequential localization of key mitotic regulators at the spindle pole and the bud neck. *Microbiology* 148: 2647-2659.

Bardin AJ, Amon A (2001) Men and sin: what's the difference? *Nature Rev Mol Cell Biol.* 2: 815-826.

McCullum D, Gould KL (2001) Timing is everything: regulation of mitotic exit and cytokinesis by the MEN and SIN. *Trends Cell Biol.* 11: 89-95.

Nilsson I, Hoffmann I. (2000) Cell cycle regulation by the Cdc25 phosphatase family. *Prog Cell Cycle Res.* 4: 107-114.

Takizawa CG, Morgan DO (2000) Control of mitosis by changes in the subcellular location of cyclin-B1-Cdk1 and Cdc25C. *Curr Opin Cell Biol.* 12: 658-665.

Ohi R, Gould KL. (1999) Regulating the onset of mitosis. *Curr Opin Cell Biol.* 11: 267-273.

Cell Cycle Checkpoints and Tumor Suppressors:

Wang X, Zou L, Lu T, Bao S, Hurov KE, Hittelman WN, Elledge SJ, Li L (2006) Rad17 phosphorylation is required for claspin recruitment and Chk1 activation in response to replication stress. *Mol. Cell* 23: 331-341.

Lin SY, Rai R, Li K, Xu ZX, Elledge SJ. (2005) BRIT1/MCPH1 is a DNA damage responsive protein that regulates the Brca1-Chk1 pathway, implicating checkpoint dysfunction in microcephaly. *Proc. Natl. Acad. Sci. USA* 102: 15105-15109.

Cortez D, Glick G, Elledge SJ (2004) Minichromosome maintenance proteins are direct targets of the ATM and ATR checkpoint kinases. *Proc. Natl. Acad. Sci. USA* 101: 10078-10083.

Kastan MB, Bartek J (2004) Cell-cycle checkpoints and cancer. *Nature* 432: 316-323.

Lowe SW, Cepero E, Evan G (2004) Intrinsic tumour suppression. *Nature* 432: 307-315.

Sugimoto M, Kuo ML, Roussel MF, Sherr CJ (2003) Nucleolar Arf tumor suppressor inhibits ribosomal RNA processing. *Mol. Cell* 11: 415-424.

Nyberg KA, Michelson RJ, Putnam CW, Weinert TA (2002) Toward maintaining the genome: DNA damage and replication checkpoints. *Annu Rev Genet.* 36: 617-656.

Winey M, Huneycutt BJ (2002) Centrosomes and checkpoints: the MPS1 family of kinases. *Oncogene.* 21: 6161-6169.

Alcasabas AA, Osborn AJ, Bachant J, Hu F, Werler PJ, Bousset K, Furuya K, Diffley JF, Carr AM, Elledge SJ (2001) Mrc1 transduces signals of DNA replication stress to activate Rad53. *Nature Cell Biol.* 3: 958-965.

Cortez D, Guntuku S, Qin J, Elledge SJ (2001) ATR and ATRIP: Partners in Checkpoint Signaling. *Science* 294: 1713-1716.

Clarke DJ, Gimenez-Abian JF (2000) Checkpoints controlling mitosis. *Bioessays.* 22: 351-363.

Lew DJ. (2000) Cell-cycle checkpoints that ensure coordination between nuclear and cytoplasmic events in *Saccharomyces cerevisiae*. *Curr Opin Genet Dev.* 10: 47-53.

Gardner RD, Burke DJ. (2000) The spindle checkpoint: two transitions, two pathways. *Trends Cell Biol.* 10: 154-158.

Rhind N, Russell P (2000) Checkpoints: it takes more than time to heal some wounds. *Curr Biol.* 10: R908-R911.

Zhou BB, Elledge SJ. (2000) The DNA damage response: putting checkpoints in perspective. *Nature* 408: 433-439.

Lowndes NF, Murguia JR. (2000) Sensing and responding to DNA damage. *Curr Opin Genet Dev.* 10: 17-25.

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pRB:

Kaye FJ. (2002) RB and cyclin dependent kinase pathways: defining a distinction between RB and p16 loss in lung cancer. *Oncogene* 21: 6908-6914.

Claudio PP, Tonini T, Giordano A (2002) The retinoblastoma family: twins or distant cousins? *Genome Biol* 3: 3012.1-3012.9.

Zheng L, Lee WH (2001) The retinoblastoma gene: a prototypic and multifunctional tumor suppressor. *Exp Cell Res.* 264: 2-18.

Nevins JR (2001) The Rb/E2F pathway and cancer. *Hum Mol Genet.* 10: 699-703.

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p53 (General Background):

Sherr CJ, McCormick F (2002) The RB and p53 pathways in cancer. *Cancer Cell* 2: 103-112.

Singh B, Reddy PG, Goberdhan A, Walsh C, Dao S, Ngai I, Chou TC, O-Charoenrat P, Levine AJ, Rao PH, Stoffel A (2002) p53 regulates cell survival by inhibiting PIK3CA in squamous cell carcinomas. *Genes Dev.* 16: 984-993.

Sherr CJ. (2001) Parsing Ink4a/Arf: "pure" p16-null mice. *Cell* 106: 531-534.

Sherr CJ, Weber JD. (2000) The ARF/p53 pathway. *Curr Opin Genet Dev.* 10: 94-99.

Weber JD, Jeffers JR, Rehg JE, Randle DH, Lozano G, Roussel MF, Sherr CJ, Zambetti GP (2000) p53-independent functions of the p19(ARF) tumor suppressor. *Genes Dev.* 14: 2358-2365.

Prives C, Hall PA. (1999) The p53 pathway. *J Pathol.* 187: 112-126.

CDK Inhibitors:

Vidal A, Koff A (2000) Cell-cycle inhibitors: three families united by a common cause. *Gene.* 247: 1-15.

Sherr CJ, Roberts JM. (1999) CDK inhibitors: positive and negative regulators of G1-phase progression. *Genes Dev.* 13: 1501-1512.

Hengst L, Reed SI. (1998) Inhibitors of the Cip/Kip family. *Current Topics Microbiol. Immunol.* 227: 25-41.

Aberrant Cell Cycle Regulation and the Molecular Basis of Cancers:

Weinberg RA (2007) *The Biology of Cancer*, Garland Science Press, New York, NY, 796pp.

Reed SI, Rothman JH (2004) Cell division, growth, and death. *Curr. Opin. Cell Biol.* 16: 599-678 (a compilation of eleven pertinent articles edited by Reed and Rothman).

Hahn WC, Weinberg RA (2002) Modelling the molecular circuitry of cancer. *Nature Rev. Cancer* 2: 331-341.

Hahn WC, Weinberg RA (2002) Rules for making human tumor cells. *N. Engl. J. Med.* 347: 1593-1603 [Erratum in: *N. Engl. J. Med.* 348: 674 (2003)]

Rajagopalan H, Bardelli A, Lengauer C, Kinzler KW, Vogelstein B, Velculescu VE (2002) Tumorigenesis: RAF/RAS oncogenes and mismatch-repair status. *Nature* 418: 934.

Sherr CJ, McCormick F (2002) The RB and p53 pathways in cancer. *Cancer Cell* 2: 103-112.

- Sherr C (2001) The INK4a/ARF network in tumour suppression. *Nature Rev. Mol. Cel. Biol.* 2: 731-737.
- Kerr P, Ashworth A (2001) New complexities for BRCA1 and BRCA2. *Curr Biol.* 11: R668-R676.
- Hanahan D, Weinberg RA (2000) The hallmarks of cancer. *Cell.* 100: 57-70.
- Sherr CJ. (2000) Cancer cell cycles revisited (Pezcoller Lecture). *Cancer Res.* 60: 3689-3695.
- Chin L, DePinho RA (2000) Flipping the oncogene switch: illumination of tumor maintenance and regression. *Trends Genet.* 16: 147-150.
- McCormick F. (1999) Signalling networks that cause cancer. *Trends Cell Biol.* 9: M53-M56.
- Ford HL, Pardee AB (1999) Cancer and the cell cycle. *J Cell Biochem.* 32-33 Suppl.: 166-172.
- Cahill DP, Kinzler KW, Vogelstein B, Lengauer C. (1999) Genetic instability and darwinian selection in tumours. *Trends Cell Biol.* 9: M57-M60.

Apoptosis (Programmed and Induced Cell Death):

- Shi Y. (2006) Mechanical aspects of apoptosome assembly. *Curr. Opin. Cell Biol.* 18: 677-684.
- Cory S, Adams JM (2005) Killing cancer cells by flipping the Bcl-2/Bax switch. *Cancer Cell* 8: 5-6.
- Holcik M, Sonenberg N. (2005) Translational control in stress and apoptosis. *Nature Rev. Mol. Cell Biol.* 6: 318-327.
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- Shi Y (2002) Mechanisms of caspase activation and inhibition during apoptosis. *Mol. Cell* 9: 459-470.
- Bouillet P, Strasser A (2002) BH3-only proteins - evolutionarily conserved proapoptotic Bcl-2 family members essential for initiating programmed cell death. *J Cell Sci* 115: 1567-1574.
- Shi Y (2001) A structural view of mitochondria-mediated apoptosis. *Nature Struct Biol.* 8: 394-401.
- Olson M, Kornbluth S (2001) Mitochondria in apoptosis and human disease. *Curr Mol Med.* 1: 91-122.
- Strasser A, O'Connor L, Dixit VM (2000) Apoptosis signaling. *Annu. Rev. Biochem.* 69: 217-245.
- Hengartner MO (2000) The biochemistry of apoptosis. *Nature.* 407: 770-776.
- Earnshaw WC, Martins LM, Kaufmann SH. (1999) Mammalian caspases: structure, activation, substrates, and functions during apoptosis. *Annu Rev Biochem.* 68: 383-424.
- Budihardjo I, Oliver H, Lutter M, Luo X, Wang X. (1999) Biochemical pathways of caspase activation during apoptosis. *Annu Rev Cell Dev Biol.* 15: 269-290.
- Gross A, McDonnell JM, Korsmeyer SJ. (1999) BCL-2 family members and the mitochondria in apoptosis. *Genes Dev.* 13: 1899-1911.
- Metzstein MM, Stanfield GM, Horvitz HR. (1998) Genetics of programmed cell death in *C. elegans*: past, present and future. *Trends Genet.* 14: 410-416.
- Raff, M. (1998) Cell suicide for beginners. *Nature* 396: 119-122.

Anti-Cancer Drug Design:

- Noble ME, Endicott JA, Johnson LN. (2004) Protein kinase inhibitors: insights into drug design from structure. *Science* 303: 1800-1805.
- Sawyers CL (2004) Targeted cancer therapy. *Nature.* 2004 432: 294-297.

- Reed JC (2001) Apoptosis-regulating proteins as targets for drug discovery. *Trends Mol Med.* 7: 314-319.
- Crews CM, Mohan R (2000) Small-molecule inhibitors of the cell cycle. *Curr Opin Chem Biol.* 4: 47-53.
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- McCormick F (2000) Small-molecule inhibitors of cell signaling. *Curr Opin Biotechnol.* 11: 593-597. Review.
- Gray N, Detivaud L, Doerig C, Meijer L. (1999) ATP-site directed inhibitors of cyclin-dependent kinases. *Curr Med Chem.* 6: 859-875.
- Noble ME, Endicott JA. (1999) Chemical inhibitors of cyclin-dependent kinases: insights into design from X-ray crystallographic studies. *Pharmacol Ther.* 82: 269-278.
- Chang YT, Gray NS, Rosania GR, Sutherlin DP, Kwon S, Norman TC, Sarohia R, Leost M, Meijer L, Schultz PG (1999) Synthesis and application of functionally diverse 2,6,9-trisubstituted purine libraries as CDK inhibitors. *Chem Biol.* 6: 361-375.
- Gray NS, Wodicka L, Thunnissen AM, Norman TC, Kwon S, Espinoza FH, Morgan DO, Barnes G, LeClerc S, Meijer L, Kim SH, Lockhart DJ, Schultz PG (1998) Exploiting chemical libraries, structure, and genomics in the search for kinase inhibitors. *Science* 281: 533-538.