

Curso de Doctorado 2005-2006
CNIO-UAM

Ciclo Celular y Cáncer

40 horas lectivas

Coordinadores:

Mariano Barbacid, Marcos Malumbres y Manuel Serrano

Lugar:

Auditorium, Centro Nacional de Investigaciones Oncológicas
Melchor Fernández Almagro 3, 28029 Madrid

Febrero 2006

Lunes 13

10:00 Introducción al ciclo celular: Bases moleculares
Marcos Malumbres, *Centro Nacional de Investigaciones Oncológicas, Madrid*

12:00 MAPK, transducción de señales y ciclo celular
Angel R. Nebreda, *Centro Nacional de Investigaciones Oncológicas, Madrid*

Martes 14

10:00 Entrada en el ciclo celular: Regulación de las Cdks
Marcos Malumbres, *Centro Nacional de Investigaciones Oncológicas, Madrid*

12:00 Replicación del ADN
Juan Mendez, *Centro Nacional de Investigaciones Oncológicas, Madrid*

Miércoles 15

10:00 Reparación del ADN
Oskar Fernández-Capetillo, *Centro Nacional de Investigaciones Oncológicas, Madrid*

12:00 Telómeros y telomerasa
María A. Blasco, *Centro Nacional de Investigaciones Oncológicas, Madrid*

Jueves 16

10:00 Transducción de señales, PI3K y ciclo celular
Amancio Carnero, *Centro Nacional de Investigaciones Oncológicas, Madrid*

12:00 Conservación del ciclo celular: de levaduras a mamíferos; visión histórica
Sergio Moreno, *Centro de Investigación del Cáncer, Salamanca*

Viernes 17

10:00 Checkpoints I: Detección y respuesta al daño en el DNA
Manuel Serrano, *Centro Nacional de Investigaciones Oncológicas, Madrid*

12:00 Checkpoints II: La ruta de p53
Manuel Serrano, *Centro Nacional de Investigaciones Oncológicas, Madrid*

Lunes 20

10:00 Regulación molecular de la mitosis
Guillermo de Cárcer, *Centro Nacional de Investigaciones Oncológicas, Madrid*

12:00 Regulación estructural de la mitosis
Ana Losada, *Centro Nacional de Investigaciones Oncológicas, Madrid*

Martes 21

10:00 Alteraciones del ciclo celular en tumores humanos
Miguel Ángel Piris, *Centro Nacional de Investigaciones Oncológicas, Madrid*

12:00 Myc: proliferación, apoptosis y el ciclo celular
Ignacio Moreno de Alborán, *Centro Nacional de Biotecnología, Madrid*

Miércoles 22

10:00 Análisis genético del ciclo celular: modelos animales
Mariano Barbacid, *Centro Nacional de Investigaciones Oncológicas, Madrid*

12:00 Implicaciones del ciclo celular en pronóstico del cáncer
Félix Bonilla, *Clínica Puerta del Hierro, Madrid*

Jueves 23

10:00 Journal Club: Bases Moleculares del ciclo celular I
Presentaciones de los alumnos

12:00 Journal Club: Bases Moleculares del ciclo celular I
Presentaciones de los alumnos

Viernes 24

10:00 Journal Club: Checkpoints
Presentaciones de los alumnos

12:00 Journal Club: Ciclo celular y cáncer humano
Presentaciones de los alumnos

Referencias

Retinoblastoma y regulación de las Cdk

M. Malumbres

Dick FA, Dyson N. pRB contains an E2F1-specific binding domain that allows E2F1-induced apoptosis to be regulated separately from other E2F activities. *Mol Cell*. 2003 Sep; 12(3): 639-49.

Wikonkal NM, Remenyik E, Knezevic D, Zhang W, Liu M, Zhao H, Berton TR, Johnson DG, Brash DE. Inactivating E2f1 reverts apoptosis resistance and cancer sensitivity in Trp53-deficient mice. *Nat Cell Biol*. 2003 Jul; 5(7): 655-60.

Hallstrom TC, Nevins JR. Specificity in the activation and control of transcription factor E2F-dependent apoptosis. *Proc Natl Acad Sci U S A*. 2003 Sep 16; 100(19): 10848-53.

Maude SL, Enders GH. Cdk inhibition in human cells compromises chk1 function and activates a DNA damage response. *Cancer Res*. 2005 Feb 1;65(3):780-6.

Jascur T, Brickner H, Salles-Passador I, Barbier V, El Khissiin A, Smith B, Fotedar R, Fotedar A. Regulation of p21(WAF1/CIP1) Stability by WISp39, a Hsp90 Binding TPR Protein. *Mol Cell*. 2005 Jan 21;17(2):237-49.

Baldassarre G, Belletti B, Nicoloso MS, Schiappacassi M, Vecchione A, Spessotto P, Morrione A, Canzonieri V, Colombatti A. p27(Kip1)-stathmin interaction influences sarcoma cell migration and invasion. *Cancer Cell*. 2005 Jan;7(1):51-63.

MAPK, transducción de señales y ciclo celular

A. Nebreda

Chou S, Huang L, Liu H. Fus3-regulated Tec1 degradation through SCFCdc4 determines MAPK signaling specificity during mating in yeast. *Cell*. 2004 Dec 29;119(7):981-90.

Escote X, Zapater M, Clotet J, Posas F. Hog1 mediates cell-cycle arrest in G1 phase by the dual targeting of Sic1. *Nat Cell Biol*. 2004 Oct;6(10):997-1002.

Manke IA, Nguyen A, Lim D, Stewart MQ, Elia AE, Yaffe MB. MAPKAP kinase-2 is a cell cycle checkpoint kinase that regulates the G2/M transition and S phase progression in response to UV irradiation. *Mol Cell*. 2005 Jan 7;17(1):37-48.

Murphy LO, Smith S, Chen RH, Fingar DC, Blenis J. Molecular interpretation of ERK signal duration by immediate early gene products. *Nat Cell Biol*. 2002 Aug;4(8):556-64.

Replicación del ADN

J. Méndez

Giordano-Coltart J, Ying CY, Gautier J, Hurwitz J (2005). Studies of the properties of human origin recognition complex and its Walker A motif mutants. *Proc Natl Acad Sci USA* 102, 69-74.

Shechter D, Costanzo V, Gautier J (2004). ATR and ATM regulate the timing of DNA replication origin firing. *Nat Cell Biol* 6, 648-655.

Eckholm-Reed S, Méndez J, Tedesco D, Zetterberg A, Stillman B, Reed SI (2004). Deregulation of cyclin E in human cells interferes with prereplication complex assembly. *J. Cell Biol.* 165, 789-800.

Bowers JL, Randell JCW, Chen S, Bell SP (2004). ATP hydrolysis by ORC catalyzes reiterative Mcm2-7 assembly at a defined origin of replication. *Mol Cell* 16, 967-978.

Reparación del ADN

O. Fernández-Capetillo

Interfaces between the detection, signaling, and repair of DNA damage. Rouse J, Jackson SP. *Science*. 2002 Jul 26;297(5581):547-51.

The role of DNA breaks in genomic instability and tumorigenesis. Mills KD, Ferguson DO, Alt FW. *Immunol Rev*. 2003 Aug;194:77-95.

Linking histone deacetylation with the repair of DNA breaks. Fernandez-Capetillo O, Nussenzweig A. *Proc Natl Acad Sci U S A*. 2004 Feb 10;101(6):1427-8. Epub 2004 Feb 02.

DNA damage activates ATM through intermolecular autophosphorylation and dimer dissociation. Bakkenist CJ, Kastan MB. *Nature*. 2003 Jan 30;421(6922):499-506.

Telómeros y telomerasa

M. A. Blasco

Garcia-Cao M, O'Sullivan R, Peters AH, Jenuwein T, Blasco MA. Epigenetic regulation of telomere length in mammalian cells by the Suv39h1 and Suv39h2 histone methyltransferases. *Nat Genet*. 2004 Jan; 36(1): 94-9. Epub 2003 Dec 14.

Seger YR, Garcia-Cao M, Piccinin S, Cunsolo CL, Doglioni C, Blasco MA, Hannon GJ, Maestro R. Transformation of normal human cells in the absence of telomerase activation. *Cancer Cell*. 2002 Nov; 2(5): 401-13.

Masutomi K, Yu EY, Khurts S, Ben-Porath I, Currier JL, Metz GB, Brooks MW, Kaneko S, Murakami S, DeCaprio JA, Weinberg RA, Stewart SA, Hahn WC. Telomerase maintains telomere structure in normal human cells. *Cell*. 2003 Jul 25; 114(2): 241-53.

Transducción de señales, PI3K y ciclo celular

A. Carnero

Bondeva, T., Pirola, L., Bulgarelli-Leva, G., Rubio, I., Wetzker, R. and Wymann, M. P. (1998). Bifurcation of lipid and protein kinase signals of PI3Kgamma to the protein kinases PKB and MAPK. *Science* 282, 293-6.

Brunet, A., Bonni, A., Zigmond, M. J., Lin, M. Z., Juo, P., Hu, L. S., Anderson, M. J., Arden, K. C., Blenis, J. and Greenberg, M. E. (1999). Akt promotes cell survival by phosphorylating and inhibiting a Forkhead transcription factor. *Cell* 96, 857-68.

Kang S, Bader AG, Vogt PK. Phosphatidylinositol 3-kinase mutations identified in human cancer are oncogenic. *Proc Natl Acad Sci U S A*. 2005;102(3):802-7.

Alvarez B, Martinez-A C, Burgering BM, Carrera AC. Forkhead transcription factors contribute to execution of the mitotic programme in mammals. *Nature*. 2001 Oct 18;413(6857):744-7.

Yu C, Rahmani M, Dai Y, Conrad D, Krystal G, Dent P, Grant S. The lethal effects of pharmacological cyclin-dependent kinase inhibitors in human leukemia cells proceed through a phosphatidylinositol 3-kinase/Akt-dependent process. *Cancer Res*. 2003 63:1822-33.

Shin I, Yakes FM, Rojo F, Shin NY, Bakin AV, Baselga J, Arteaga CL. PKB/Akt mediates cell-cycle progression by phosphorylation of p27(Kip1) at threonine 157 and modulation of its cellular localization. *Nat Med*. 2002 Oct;8(10):1145-52. Epub 2002 Sep 16.

Kauffmann-Zeh, A., Rodriguez-Viciano, P., Ulrich, E., Gilbert, C., Coffey, P., Downward, J. and Evan, G. (1997). Suppression of c-Myc-induced apoptosis by Ras signalling through PI(3)K and PKB. *Nature* 385, 544-8.

Checkpoints

M. Serrano

Villunger A, Michalak EM, Coultas L, Mullauer F, Bock G, Ausserlechner MJ, Adams JM, Strasser A. p53- and drug-induced apoptotic responses mediated by BH3-only proteins puma and noxa. *Science*. 2003 Nov 7; 302(5647): 1036-8.

Vassilev LT, Vu BT, Graves B, Carvajal D, Podlaski F, Filipovic Z, Kong N, Kammlott U, Lukacs C, Klein C, Fotouhi N, Liu EA. In Vivo Activation of the p53 Pathway by Small-Molecule Antagonists of MDM2. *Science*. 2004

Garcia-Cao I, Garcia-Cao M, Martin-Caballero J, Criado LM, Klatt P, Flores JM, Weill JC, Blasco MA, Serrano M. "Super p53" mice exhibit enhanced DNA damage response, are tumor resistant and age normally. *EMBO J*. 2002 Nov 15; 21(22): 6225-35.

Mitosis

G. de Cárcer

Tsurumi C, Hoffmann S, Geley S, Graeser R, Polanski Z. The spindle assembly checkpoint is not essential for CSF arrest of mouse oocytes. *J Cell Biol*. 2004 Dec 20;167(6):1037-50.

Kraft C, Herzog F, Gieffers C, Mechtler K, Hagting A, Pines J, Peters JM. Mitotic regulation of the human anaphase-promoting complex by phosphorylation. *EMBO J*. 2003 Dec 15;22(24):6598-609.

Hauf S, Cole RW, LaTerra S, Zimmer C, Schnapp G, Walter R, Heckel A, van Meel J, Rieder CL, Peters JM. The small molecule Hesperadin reveals a role for Aurora B in correcting kinetochore-microtubule attachment and in maintaining the spindle assembly checkpoint. *J Cell Biol*. 2003 Apr 28;161(2):281-94. Epub 2003 Apr 21.

Topper LM, Campbell MS, Tugendreich S, Daum JR, Burke DJ, Hieter P, Gorbsky GJ. The dephosphorylated form of the anaphase-promoting complex protein Cdc27/Apc3 concentrates on kinetochores and chromosome arms in mitosis. *Cell Cycle*. 2002 Jul-Aug;1(4):282-92.

Mitosis

A. Losada

Ono T, Losada A, Hirano M, Myers MP, Neuwald AF, Hirano T. "Differential contributions of condensin I and condensin II to mitotic chromosome architecture in vertebrate cells". (2003) *Cell* 115:109-21.

Losada A, Hirano M, Hirano T. "Cohesin release is required for sister chromatid resolution, but not for condensin-mediated compaction, at the onset of mitosis." (2002) *Genes Dev*. 16: 3004-16.

Gruber S, Haering CH, Nasmyth K. "Chromosomal cohesin forms a ring". (2003) *Cell* 112:765-77.

Andrews PD, Ovechkina Y, Morrice N, Wagenbach M, Duncan K, Wordeman L and Swedlow JR "Aurora B regulates MCAK at the mitotic centromere". (2004) *Dev. Cell* 6: 253-268.

Hall IM, Noma K, Grewal SI. "RNA interference machinery regulates chromosome dynamics during mitosis and meiosis in fission yeast". (2003) *Proc Natl Acad Sci U S A*. 100:193-8.

Análisis genético del ciclo celular: modelos animales

M. Barbacid

Malumbres M, Sotillo R, Santamaria D, Galan J, Cerezo A, Ortega S, Dubus P, Barbacid M. Mammalian cells cycle without the D-type cyclin-dependent kinases Cdk4 and Cdk6. *Cell*. 118:493-504, 2004.

Kozar K, Ciemerych MA, Rebel VI, Shigematsu H, Zagozdzon A, Sicinska E, Geng Y, Yu Q, Bhattacharya S, Bronson RT, Akashi K, Sicinski P. Mouse development and cell proliferation in the absence of D-cyclins. *Cell*. 118:477-491, 2004.

Ortega S, Prieto I, Odajima J, Martin A, Dubus P, Sotillo R, Barbero JL, Malumbres M, Barbacid M. Cyclin-dependent kinase 2 is essential for meiosis but not for mitotic cell division in mice. *Nat Genet*. 35:25-31 (2003).

Geng Y, Yu Q, Sicinska E, Das M, Schneider JE, Bhattacharya S, Rideout WM, Bronson RT, Gardner H, Sicinski P. Cyclin E ablation in the mouse. *Cell*. 114:431-443, 2003.

Yu Q, Geng Y, Sicinski P. Specific protection against breast cancers by cyclin D1 ablation. *Nature*. 411:1017-1021, 2001.

Geng Y, Whoriskey W, Park MY, Bronson RT, Medema RH, Li T, Weinberg RA, Sicinski P. Rescue of cyclin D1 deficiency by knockin cyclin E. *Cell*. 97:767-777, 1999.

Myc: proliferación, apoptosis y el ciclo celular

I. Moreno de Alborán

Wilson, A., M.J. Murphy, T. Oskarsson, K. Kaloulis, M.D. Bettess, G.M. Oser, A.C. Pasche, C. Knabenhans, H.R. Macdonald, and A. Trumpp. 2004. c-Myc controls the balance between hematopoietic stem cell self-renewal and differentiation. *Genes Dev* **18**: 2747-63.

Shachaf, C.M., A.M. Kopelman, C. Arvanitis, A. Karlsson, S. Beer, S. Mandl, M.H. Bachmann, A.D. Borowsky, B. Ruebner, R.D. Cardiff, Q. Yang, J.M. Bishop, C.H. Contag, and D.W. Felsher. 2004. MYC inactivation uncovers pluripotent differentiation and tumour dormancy in hepatocellular cancer. *Nature* **431**: 1112-7.

Malynn B. A., Moreno de Alboran I., O'Hagan R.C., Bronson R., Davidson L., DePinho R.A. and F.W. aA (2000) N-myc can functionally replace c-myc in murine development, cellular growth, and differentiation. *Genes Dev* **14**: 1390-1399.

Moreno, E., and Basler, K. (2004). dMyc transforms cells into super-competitors. *Cell* **117**, 117-129.

Alteraciones del ciclo celular en tumores humanos

M.A. Piris

Sanchez-Aguilera A, Delgado J, Camacho FI, Sanchez-Beato M, Sanchez L, Montalban C, Fresno MF, Martin C, Piris MA, Garcia JF. Silencing of the p18INK4c gene by promoter hypermethylation in the Reed-Sternberg cells in Hodgkin Lymphomas. *Blood*. 2004 Mar 15;103(6):2351-7

Garcia JF, et al. Spanish Hodgkin Lymphoma Study Group. Hodgkin and Reed-Sternberg cells harbor alterations in the major tumor suppressor pathways and cell-cycle checkpoints: analyses using tissue microarrays. *Blood*. 2003 Jan 15; 101(2): 681-9.

Sanchez-Beato M, Sanchez-Aguilera A, Piris MA. Cell cycle deregulation in B-cell lymphomas. *Blood*. 2003 Feb 15; 101(4): 1220-35. Epub 2002 Sep 12.

Implicaciones del ciclo celular en pronóstico del cáncer

F. Bonilla

Keyomarsi K, et al. Cyclin E and survival in patients with breast cancer. *New Engl J Med*. 347: 1566-1575; 2002

Van de Vijver MJ et al. A gene-expression signature as a predictor of survival in breast cancer. *New Engl J Med*. 347: 1999-2009; 2002

Lossos IS, et al. Prediction of survival in diffuse large-B-cell lymphoma based on the expression of six genes. *New Engl J Med*. 350: 1828-1837; 2004

Cappuzzo F et al. Akt phosphorylation and Gefitinib efficacy in patients with advanced non-small-cell lung cancer. *J Nat Cancer Inst*. 96: 1133-1141; 2004

Jansen MP. et al. Molecular classification of Tamoxifen-resistant breast carcinomas by gene expression profiling. *J Clin Oncol*. 23: 732-740; 2005