

Estudio de las vías de supervivencia y muerte neuronal en modelos de la enfermedad de Huntington

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Departamento de
Biología Celular, Inmunología y Neurociencias
Facultad de Medicina

ESTUDIO DE LAS VÍAS DE SUPERVIVENCIA Y MUERTE NEURONAL EN MODELOS DE LA ENFERMEDAD DE HUNTINGTON

**Tesis presentada por Paola Paoletti Rubia
para optar al título de Doctora por la Universidad de Barcelona**

Programa de Doctorado en Biomedicina

VI. BIBLIOGRAFÍA

- Aebischer P, Ridet J (2001) Recombinant proteins for neurodegenerative diseases: the delivery issue. *Trends Neurosci* 24: 533-540.
- Airaksinen MS, Saarma M (2002) The GDNF family: signalling, biological functions and therapeutic value. *Nat Rev Neurosci* 3: 383-394.
- Alberch J, Perez-Navarro E, Canals JM (2004) Neurotrophic factors in Huntington's disease. *Prog Brain Res* 146: 195-229.
- Albin RL, Gilman S (1990) Autoradiographic localization of inhibitory and excitatory amino acid neurotransmitter receptors in human normal and olivopontocerebellar atrophy cerebellar cortex. *Brain Res* 522: 37-45.
- Albin RL, Reiner A, Anderson KD, Dure LS, Handelin B, Balfour R, Whetsell WO, Jr., Penney JB, Young AB (1992) Preferential loss of striato-external pallidal projection neurons in presymptomatic Huntington's disease. *Ann Neurol* 31: 425-430.
- Alessi DR, Cohen P (1998) Mechanism of activation and function of protein kinase B. *Curr Opin Genet Dev* 8: 55-62.
- Alexi T, Borlongan CV, Faull RL, Williams CE, Clark RG, Gluckman PD, Hughes PE (2000) Neuroprotective strategies for basal ganglia degeneration: Parkinson's and Huntington's diseases. *Prog Neurobiol* 60: 409-470.
- Allan LA, Morrice N, Brady S, Magee G, Pathak S, Clarke PR (2003) Inhibition of caspase-9 through phosphorylation at Thr 125 by ERK MAPK. *Nat Cell Biol* 5: 647-654.
- Alonso A, Sasin J, Bottini N, Friedberg I, Friedberg I, Osterman A, Godzik A, Hunter T, Dixon J, Mustelin T (2004) Protein tyrosine phosphatases in the human genome. *Cell* 117: 699-711.
- Anne SL, Saudou F, Humbert S (2007) Phosphorylation of huntingtin by cyclin-dependent kinase 5 is induced by DNA damage and regulates wild-type and mutant huntingtin toxicity in neurons. *J Neurosci* 27: 7318-7328.
- Apostol BL, Illes K, Pallos J, Bodai L, Wu J, Strand A, Schweitzer ES, Olson JM, Kazantsev A, Marsh JL, Thompson LM (2006) Mutant huntingtin alters MAPK signaling pathways in PC12 and striatal cells: ERK1/2 protects against mutant huntingtin-associated toxicity. *Hum Mol Genet* 15: 273-285.
- Arden KC, Biggs WH, III (2002) Regulation of the FoxO family of transcription factors by phosphatidylinositol-3 kinase-activated signaling. *Arch Biochem Biophys* 403: 292-298.
- Arevalo JC, Wu SH (2006) Neurotrophin signaling: many exciting surprises! *Cell Mol Life Sci* 63: 1523-1537.
- Arnaout MA, Goodman SL, Xiong JP (2007) Structure and mechanics of integrin-based cell adhesion. *Curr Opin Cell Biol* 19: 495-507.
- Arrasate M, Mitra S, Schweitzer ES, Segal MR, Finkbeiner S (2004) Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. *Nature* 431: 805-810.

BIBLIOGRAFÍA

- Augood SJ, Faull RL, Emson PC (1997) Dopamine D1 and D2 receptor gene expression in the striatum in Huntington's disease. *Ann Neurol* 42: 215-221.
- Aznar S, Valeron PF, del Rincon SV, Perez LF, Perona R, Lacal JC (2001) Simultaneous tyrosine and serine phosphorylation of STAT3 transcription factor is involved in Rho A GTPase oncogenic transformation. *Mol Biol Cell* 12: 3282-3294.
- Baas PW (1999) Microtubules and neuronal polarity: lessons from mitosis. *Neuron* 22: 23-31.
- Bae BI, Xu H, Igarashi S, Fujimuro M, Agrawal N, Taya Y, Hayward SD, Moran TH, Montell C, Ross CA, Snyder SH, Sawa A (2005) p53 mediates cellular dysfunction and behavioral abnormalities in Huntington's disease. *Neuron* 47: 29-41.
- Bajaj NP, Al Sarraj ST, Anderson V, Kibble M, Leigh N, Miller CC (1998) Cyclin-dependent kinase-5 is associated with lipofuscin in motor neurones in amyotrophic lateral sclerosis. *Neurosci Lett* 245: 45-48.
- Ballif BA, Blenis J (2001) Molecular mechanisms mediating mammalian mitogen-activated protein kinase (MAPK) kinase (MEK)-MAPK cell survival signals. *Cell Growth Differ* 12: 397-408.
- Barclay JW, Aldea M, Craig TJ, Morgan A, Burgoyne RD (2004) Regulation of the fusion pore conductance during exocytosis by cyclin-dependent kinase 5. *J Biol Chem* 279: 41495-41503.
- Barria A, Malinow R (2002) Subunit-specific NMDA receptor trafficking to synapses. *Neuron* 35: 345-353.
- Bates G (2003) Huntingtin aggregation and toxicity in Huntington's disease. *Lancet* 361: 1642-1644.
- Baumann K, Mandelkow EM, Biernat J, Piwnica-Worms H, Mandelkow E (1993) Abnormal Alzheimer-like phosphorylation of tau-protein by cyclin-dependent kinases cdk2 and cdk5. *FEBS Lett* 336: 417-424.
- Bayascas JR, Alessi DR (2005) Regulation of Akt/PKB Ser473 phosphorylation. *Mol Cell* 18: 143-145.
- Bayascas JR (2008) Dissecting the role of the 3-phosphoinositide-dependent protein kinase-1 (PDK1) signalling pathways. *Cell Cycle* 7: 2978-2982.
- Beal MF, Kowall NW, Ellison DW, Mazurek MF, Swartz KJ, Martin JB (1986) Replication of the neurochemical characteristics of Huntington's disease by quinolinic acid. *Nature* 321: 168-171.
- Beal MF, Kowall NW, Swartz KJ, Ferrante RJ, Martin JB (1989) Differential sparing of somatostatin-neuropeptide Y and cholinergic neurons following striatal excitotoxin lesions. *Synapse* 3: 38-47.
- Becher MW, Kotzuk JA, Sharp AH, Davies SW, Bates GP, Price DL, Ross CA (1998) Intranuclear neuronal inclusions in Huntington's disease and dentatorubral and

- pallidolysian atrophy: correlation between the density of inclusions and IT15 CAG triplet repeat length. *Neurobiol Dis* 4: 387-397.
- Benchoua A, Trioulier Y, Diguet E, Malgorn C, Gaillard MC, Dufour N, Elalouf JM, Krajewski S, Hantraye P, Deglon N, Brouillet E (2008) Dopamine determines the vulnerability of striatal neurons to the N-terminal fragment of mutant huntingtin through the regulation of mitochondrial complex II. *Hum Mol Genet* 17: 1446-1456.
- Berliocchi L, Bano D, Nicotera P (2005) Ca²⁺ signals and death programmes in neurons. *Philos Trans R Soc Lond B Biol Sci* 360: 2255-2258.
- Bhide PG, Day M, Sapp E, Schwarz C, Sheth A, Kim J, Young AB, Penney J, Golden J, Aronin N, DiFiglia M (1996) Expression of normal and mutant huntingtin in the developing brain. *J Neurosci* 16: 5523-5535.
- Bibb JA, Yan Z, Svenssonsson P, Snyder GL, Pieribone VA, Horiuchi A, Nairn AC, Messer A, Greengard P (2000) Severe deficiencies in dopamine signaling in presymptomatic Huntington's disease mice. *Proc Natl Acad Sci U S A* 97: 6809-6814.
- Blank T, Nijholt I, Teichert U, Kugler H, Behrsing H, Fienberg A, Greengard P, Spiess J (1997) The phosphoprotein DARPP-32 mediates cAMP-dependent potentiation of striatal N-methyl-D-aspartate responses. *Proc Natl Acad Sci U S A* 94: 14859-14864.
- Blume-Jensen P, Janknecht R, Hunter T (1998) The kit receptor promotes cell survival via activation of PI 3-kinase and subsequent Akt-mediated phosphorylation of Bad on Ser136. *Curr Biol* 8: 779-782.
- Bohnen NI, Koeppe RA, Meyer P, Ficaro E, Wernette K, Kilbourn MR, Kuhl DE, Frey KA, Albin RL (2000) Decreased striatal monoaminergic terminals in Huntington disease. *Neurology* 54: 1753-1759.
- Borrell-Pages M, Zala D, Humbert S, Saudou F (2006) Huntington's disease: from huntingtin function and dysfunction to therapeutic strategies. *Cell Mol Life Sci* 63: 2642-2660.
- Brazil DP, Yang ZZ, Hemmings BA (2004) Advances in protein kinase B signalling: AKTion on multiple fronts. *Trends Biochem Sci* 29: 233-242.
- Brown NR, Noble ME, Endicott JA, Johnson LN (1999) The structural basis for specificity of substrate and recruitment peptides for cyclin-dependent kinases. *Nat Cell Biol* 1: 438-443.
- Browne SE, Beal MF (2006) Oxidative damage in Huntington's disease pathogenesis. *Antioxid Redox Signal* 8: 2061-2073.
- Brunet A, Bonni A, Zigmond MJ, Lin MZ, Juo P, Hu LS, Anderson MJ, Arden KC, Blenis J, Greenberg ME (1999) Akt promotes cell survival by phosphorylating and inhibiting a Forkhead transcription factor. *Cell* 96: 857-868.
- Buller AL, Larson HC, Schneider BE, Beaton JA, Morrisett RA, Monaghan DT (1994) The molecular basis of NMDA receptor subtypes: native receptor diversity is predicted by subunit composition. *J Neurosci* 14: 5471-5484.

BIBLIOGRAFÍA

- Burgering BM, Coffer PJ (1995) Protein kinase B (c-Akt) in phosphatidylinositol-3-OH kinase signal transduction. *Nature* 376: 599-602.
- Butterworth NJ, Williams L, Bullock JY, Love DR, Faull RL, Dragunow M (1998) Trinucleotide (CAG) repeat length is positively correlated with the degree of DNA fragmentation in Huntington's disease striatum. *Neuroscience* 87: 49-53.
- Buzko O, Shokat KM (2002) A kinase sequence database: sequence alignments and family assignment. *Bioinformatics* 18: 1274-1275.
- Canals JM, Marco S, Checa N, Michels A, Perez-Navarro E, Arenas E, Alberch J (1998) Differential regulation of the expression of nerve growth factor, brain-derived neurotrophic factor, and neurotrophin-3 after excitotoxicity in a rat model of Huntington's disease. *Neurobiol Dis* 5: 357-364.
- Canals JM, Checa N, Marco S, Michels A, Perez-Navarro E, Alberch J (1999) The neurotrophin receptors trkB, trkA and trkC are differentially regulated after excitotoxic lesion in rat striatum. *Brain Res Mol Brain Res* 69: 242-248.
- Cancino GI, Toledo EM, Leal NR, Hernandez DE, Yevenes LF, Inestrosa NC, Alvarez AR (2008) ST1571 prevents apoptosis, tau phosphorylation and behavioural impairments induced by Alzheimer's beta-amyloid deposits. *Brain* 131: 2425-2442.
- Cancino GI, Perez dA, Castro PU, Toledo EM, von Bernhardi R, Alvarez AR (2009) c-Abl tyrosine kinase modulates tau pathology and Cdk5 phosphorylation in AD transgenic mice. *Neurobiol Aging*.
- Carracedo A, Pandolfi PP (2008) The PTEN-PI3K pathway: of feedbacks and cross-talks. *Oncogene* 27: 5527-5541.
- Cattaneo E, Zuccato C, Tartari M (2005) Normal huntingtin function: an alternative approach to Huntington's disease. *Nat Rev Neurosci* 6: 919-930.
- Cavanaugh JE, Jaumotte JD, Lakoski JM, Zigmond MJ (2006) Neuroprotective role of ERK1/2 and ERK5 in a dopaminergic cell line under basal conditions and in response to oxidative stress. *J Neurosci Res* 84: 1367-1375.
- Cepeda C, Levine MS (1998) Dopamine and N-methyl-D-aspartate receptor interactions in the neostriatum. *Dev Neurosci* 20: 1-18.
- Cepeda C, Levine MS (2006) Where do you think you are going? The NMDA-D1 receptor trap. *Sci STKE* 2006: e20.
- Cha JH, Kosinski CM, Kerner JA, Alsdorf SA, Mangiarini L, Davies SW, Penney JB, Bates GP, Young AB (1998) Altered brain neurotransmitter receptors in transgenic mice expressing a portion of an abnormal human huntington disease gene. *Proc Natl Acad Sci U S A* 95: 6480-6485.
- Chae T, Kwon YT, Bronson R, Dikkes P, Li E, Tsai LH (1997) Mice lacking p35, a neuronal specific activator of Cdk5, display cortical lamination defects, seizures, and adult lethality. *Neuron* 18: 29-42.

- Chao MV (2003) Neurotrophins and their receptors: a convergence point for many signalling pathways. *Nat Rev Neurosci* 4: 299-309.
- Charvin D, Vanhoutte P, Pages C, Borrelli E, Caboche J (2005) Unraveling a role for dopamine in Huntington's disease: the dual role of reactive oxygen species and D2 receptor stimulation. *Proc Natl Acad Sci U S A* 102: 12218-12223.
- Checa N, Canals JM, Alberch J (2000) Developmental regulation of BDNF and NT-3 expression by quinolinic acid in the striatum and its main connections. *Exp Neurol* 165: 118-124.
- Checa N, Canals JM, Gratacos E, Alberch J (2001) TrkB and TrkC are differentially regulated by excitotoxicity during development of the basal ganglia. *Exp Neurol* 172: 282-292.
- Chen BS, Roche KW (2007) Regulation of NMDA receptors by phosphorylation. *Neuropharmacology* 53: 362-368.
- Chen J, Wersinger C, Sidhu A (2003) Chronic stimulation of D1 dopamine receptors in human SK-N-MC neuroblastoma cells induces nitric-oxide synthase activation and cytotoxicity. *J Biol Chem* 278: 28089-28100.
- Chen J, Rusnak M, Luedtke RR, Sidhu A (2004) D1 dopamine receptor mediates dopamine-induced cytotoxicity via the ERK signal cascade. *J Biol Chem* 279: 39317-39330.
- Chen J, Rusnak M, Lombroso PJ, Sidhu A (2009) Dopamine promotes striatal neuronal apoptotic death via ERK signaling cascades. *Eur J Neurosci* 29: 287-306.
- Chen Q, Reiner A (1996) Cellular distribution of the NMDA receptor NR2A/2B subunits in the rat striatum. *Brain Res* 743: 346-352.
- Chen Q, Veenman CL, Reiner A (1996) Cellular expression of ionotropic glutamate receptor subunits on specific striatal neuron types and its implication for striatal vulnerability in glutamate receptor-mediated excitotoxicity. *Neuroscience* 73: 715-731.
- Chen Q, Surmeier DJ, Reiner A (1999) NMDA and non-NMDA receptor-mediated excitotoxicity are potentiated in cultured striatal neurons by prior chronic depolarization. *Exp Neurol* 159: 283-296.
- Chen Y, Zeng J, Cen L, Chen Y, Wang X, Yao G, Wang W, Qi W, Kong K (2009) Multiple roles of the p75 neurotrophin receptor in the nervous system. *J Int Med Res* 37: 281-288.
- Cheng K, Ip NY (2003) Cdk5: a new player at synapses. *Neurosignals* 12: 180-190.
- Cheung EC, Slack RS (2004) Emerging role for ERK as a key regulator of neuronal apoptosis. *Sci STKE* 2004: E45.
- Choi DW (1988) Glutamate neurotoxicity and diseases of the nervous system. *Neuron* 1: 623-634.
- Clary DO, Reichardt LF (1994) An alternatively spliced form of the nerve growth factor receptor TrkA confers an enhanced response to neurotrophin 3. *Proc Natl Acad Sci U S A* 91: 11133-11137.

BIBLIOGRAFÍA

- Colwell CS, Levine MS (1995) Excitatory synaptic transmission in neostriatal neurons: regulation by cyclic AMP-dependent mechanisms. *J Neurosci* 15: 1704-1713.
- Corbit KC, Foster DA, Rosner MR (1999) Protein kinase C δ mediates neurogenic but not mitogenic activation of mitogen-activated protein kinase in neuronal cells. *Mol Cell Biol* 19: 4209-4218.
- Coronas V, Feron F, Hen R, Sicard G, Jourdan F, Moyse E (1997) In vitro induction of apoptosis or differentiation by dopamine in an immortalized olfactory neuronal cell line. *J Neurochem* 69: 1870-1881.
- Coyle JT, Schwarcz R (1976) Lesion of striatal neurones with kainic acid provides a model for Huntington's chorea. *Nature* 263: 244-246.
- Crespo-Biel N, Camins A, Pelegri C, Vilaplana J, Pallas M, Canudas AM (2007) 3-Nitropropionic acid activates calpain/cdk5 pathway in rat striatum. *Neurosci Lett* 421: 77-81.
- Crespo-Biel N, Camins A, Pallas M, Canudas AM (2009) Evidence of calpain/cdk5 pathway inhibition by lithium in 3-nitropropionic acid toxicity in vivo and in vitro. *Neuropharmacology* 56: 422-428.
- Cross DA, Alessi DR, Cohen P, Andjelkovich M, Hemmings BA (1995) Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B. *Nature* 378: 785-789.
- Cruz JC, Tsai LH (2004) Cdk5 deregulation in the pathogenesis of Alzheimer's disease. *Trends Mol Med* 10: 452-458.
- Cudkowicz M, Kowall NW (1990) Degeneration of pyramidal projection neurons in Huntington's disease cortex. *Ann Neurol* 27: 200-204.
- Culmsee C, Gerling N, Lehmann M, Nikolova-Karakashian M, Prehn JH, Mattson MP, Kriegstein J (2002) Nerve growth factor survival signaling in cultured hippocampal neurons is mediated through TrkB and requires the common neurotrophin receptor P75. *Neuroscience* 115: 1089-1108.
- Datta SR, Dudek H, Tao X, Masters S, Fu H, Gotoh Y, Greenberg ME (1997) Akt phosphorylation of BAD couples survival signals to the cell-intrinsic death machinery. *Cell* 91: 231-241.
- Davies SW, Turmaine M, Cozens BA, DiFiglia M, Sharp AH, Ross CA, Scherzinger E, Wanker EE, Mangiarini L, Bates GP (1997) Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation. *Cell* 90: 537-548.
- Davis RJ (2000) Signal transduction by the JNK group of MAP kinases. *Cell* 103: 239-252.
- de la Monte SM, Vonsattel JP, Richardson EP, Jr. (1988) Morphometric demonstration of atrophic changes in the cerebral cortex, white matter, and neostriatum in Huntington's disease. *J Neuropathol Exp Neurol* 47: 516-525.
- del Peso L, Gonzalez-Garcia M, Page C, Herrera R, Nunez G (1997) Interleukin-3-induced phosphorylation of BAD through the protein kinase Akt. *Science* 278: 687-689.

- del Peso L, Gonzalez VM, Hernandez R, Barr FG, Nunez G (1999) Regulation of the forkhead transcription factor FKHR, but not the PAX3-FKHR fusion protein, by the serine/threonine kinase Akt. *Oncogene* 18: 7328-7333.
- Desce JM, Godeheu G, Galli T, Artaud F, Cheramy A, Glowinski J (1992) L-glutamate-evoked release of dopamine from synaptosomes of the rat striatum: involvement of AMPA and N-methyl-D-aspartate receptors. *Neuroscience* 47: 333-339.
- Deyts C, Galan-Rodriguez B, Martin E, Bouveyron N, Roze E, Charvin D, Caboche J, Betuing S (2009) Dopamine D₂ receptor stimulation potentiates PolyQ-Huntingtin-induced mouse striatal neuron dysfunctions via Rho/ROCK-II activation. *PLoS One* 4: e8287.
- Dhariwala FA, Rajadhyaksha MS (2008) An unusual member of the Cdk family: Cdk5. *Cell Mol Neurobiol* 28: 351-369.
- Dhavan R, Tsai LH (2001) A decade of CDK5. *Nat Rev Mol Cell Biol* 2: 749-759.
- Diaz-Hernandez M, Torres-Peraza J, Salvatori-Abarca A, Moran MA, Gomez-Ramos P, Alberch J, Lucas JJ (2005) Full motor recovery despite striatal neuron loss and formation of irreversible amyloid-like inclusions in a conditional mouse model of Huntington's disease. *J Neurosci* 25: 9773-9781.
- DiFiglia M, Sapp E, Chase KO, Davies SW, Bates GP, Vonsattel JP, Aronin N (1997) Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain. *Science* 277: 1990-1993.
- Dijkers PF, Medema RH, Lammers JW, Koenderman L, Coffer PJ (2000) Expression of the pro-apoptotic Bcl-2 family member Bim is regulated by the forkhead transcription factor FKHR-L1. *Curr Biol* 10: 1201-1204.
- Dougherty MK, Muller J, Ritt DA, Zhou M, Zhou XZ, Copeland TD, Conrads TP, Veenstra TD, Lu KP, Morrison DK (2005) Regulation of Raf-1 by direct feedback phosphorylation. *Mol Cell* 17: 215-224.
- Dudek H, Datta SR, Franke TF, Birnbaum MJ, Yao R, Cooper GM, Segal RA, Kaplan DR, Greenberg ME (1997) Regulation of neuronal survival by the serine-threonine protein kinase Akt. *Science* 275: 661-665.
- Dugan LL, Sensi SL, Canzoniero LM, Handran SD, Rothman SM, Lin TS, Goldberg MP, Choi DW (1995) Mitochondrial production of reactive oxygen species in cortical neurons following exposure to N-methyl-D-aspartate. *J Neurosci* 15: 6377-6388.
- Duronio V (2008) The life of a cell: apoptosis regulation by the PI3K/PKB pathway. *Biochem J* 415: 333-344.
- Duyao M, Ambrose C, Myers R, Novelletto A, Persichetti F, Frontali M, Folstein S, Ross C, Franz M, Abbott M, et al. (1993) Trinucleotide repeat length instability and age of onset in Huntington's disease. *Nat Genet* 4: 387-392.
- Duyao MP, Auerbach AB, Ryan A, Persichetti F, Barnes GT, McNeil SM, Ge P, Vonsattel JP, Gusella JF, Joyner AL, et al. (1995) Inactivation of the mouse Huntington's disease gene homolog Hdh. *Science* 269: 407-410.

BIBLIOGRAFÍA

- Egea J, Espinet C, Soler RM, Dolcet X, Yuste VJ, Encinas M, Iglesias M, Rocamora N, Comella JX (2001) Neuronal survival induced by neurotrophins requires calmodulin. *J Cell Biol* 154: 585-597.
- Ehrhardt C, Ludwig S (2009) A new player in a deadly game: influenza viruses and the PI3K/Akt signalling pathway. *Cell Microbiol* 11: 863-871.
- Erhardt P, Schremser EJ, Cooper GM (1999) B-Raf inhibits programmed cell death downstream of cytochrome c release from mitochondria by activating the MEK/Erk pathway. *Mol Cell Biol* 19: 5308-5315.
- Estrada Sanchez AM, Mejia-Toiber J, Massieu L (2008) Excitotoxic neuronal death and the pathogenesis of Huntington's disease. *Arch Med Res* 39: 265-276.
- Fan J, Cowan CM, Zhang LY, Hayden MR, Raymond LA (2009) Interaction of postsynaptic density protein-95 with NMDA receptors influences excitotoxicity in the yeast artificial chromosome mouse model of Huntington's disease. *J Neurosci* 29: 10928-10938.
- Fan MM, Raymond LA (2007) N-methyl-D-aspartate (NMDA) receptor function and excitotoxicity in Huntington's disease. *Prog Neurobiol* 81: 272-293.
- Ferrante RJ, Kowall NW, Beal MF, Richardson EP, Jr., Bird ED, Martin JB (1985) Selective sparing of a class of striatal neurons in Huntington's disease. *Science* 230: 561-563.
- Ferrante RJ, Kowall NW, Beal MF, Martin JB, Bird ED, Richardson EP, Jr. (1987) Morphologic and histochemical characteristics of a spared subset of striatal neurons in Huntington's disease. *J Neuropathol Exp Neurol* 46: 12-27.
- Ferrante RJ, Kowall NW (1987) Tyrosine hydroxylase-like immunoreactivity is distributed in the matrix compartment of normal human and Huntington's disease striatum. *Brain Res* 416: 141-146.
- Ferrante RJ, Kowall NW, Richardson EP, Jr. (1991) Proliferative and degenerative changes in striatal spiny neurons in Huntington's disease: a combined study using the section-Golgi method and calbindin D28k immunocytochemistry. *J Neurosci* 11: 3877-3887.
- Ferrante RJ, Kowall NW, Cipolloni PB, Storey E, Beal MF (1993) Excitotoxin lesions in primates as a model for Huntington's disease: histopathologic and neurochemical characterization. *Exp Neurol* 119: 46-71.
- Ferrante RJ (2009) Mouse models of Huntington's disease and methodological considerations for therapeutic trials. *Biochim Biophys Acta* 1792: 506-520.
- Ferrer I, Goutan E, Marin C, Rey MJ, Ribalta T (2000) Brain-derived neurotrophic factor in Huntington disease. *Brain Res* 866: 257-261.
- Fiorentini C, Gardoni F, Spano P, Di Luca M, Missale C (2003) Regulation of dopamine D1 receptor trafficking and desensitization by oligomerization with glutamate N-methyl-D-aspartate receptors. *J Biol Chem* 278: 20196-20202.

- Fletcher Al, Shuang R, Giovannucci DR, Zhang L, Bittner MA, Stuenkel EL (1999) Regulation of exocytosis by cyclin-dependent kinase 5 via phosphorylation of Munc18. *J Biol Chem* 274: 4027-4035.
- Flores-Hernandez J, Cepeda C, Hernandez-Echeagaray E, Calvert CR, Jokel ES, Fienberg AA, Greengard P, Levine MS (2002) Dopamine enhancement of NMDA currents in dissociated medium-sized striatal neurons: role of D1 receptors and DARPP-32. *J Neurophysiol* 88: 3010-3020.
- Frade JM, Rodriguez-Tebar A, Barde YA (1996) Induction of cell death by endogenous nerve growth factor through its p75 receptor. *Nature* 383: 166-168.
- Franke TF, Yang SI, Chan TO, Datta K, Kazlauskas A, Morrison DK, Kaplan DR, Tsichlis PN (1995) The protein kinase encoded by the Akt proto-oncogene is a target of the PDGF-activated phosphatidylinositol 3-kinase. *Cell* 81: 727-736.
- Franke TF, Kaplan DR, Cantley LC (1997) PI3K: downstream AKTion blocks apoptosis. *Cell* 88: 435-437.
- Fu WY, Chen Y, Sahin M, Zhao XS, Shi L, Bikoff JB, Lai KO, Yung WH, Fu AK, Greenberg ME, Ip NY (2007) Cdk5 regulates EphA4-mediated dendritic spine retraction through an ephexin1-dependent mechanism. *Nat Neurosci* 10: 67-76.
- Fu X, Choi YK, Qu D, Yu Y, Cheung NS, Qi RZ (2006) Identification of nuclear import mechanisms for the neuronal Cdk5 activator. *J Biol Chem* 281: 39014-39021.
- Fukata Y, Itoh TJ, Kimura T, Menager C, Nishimura T, Shiromizu T, Watanabe H, Inagaki N, Iwamatsu A, Hotani H, Kaibuchi K (2002) CRMP-2 binds to tubulin heterodimers to promote microtubule assembly. *Nat Cell Biol* 4: 583-591.
- 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.
- Fukunaga K, Miyamoto E (1998) Role of MAP kinase in neurons. *Mol Neurobiol* 16: 79-95.
- Gao T, Furnari F, Newton AC (2005) PHLPP: a phosphatase that directly dephosphorylates Akt, promotes apoptosis, and suppresses tumor growth. *Mol Cell* 18: 13-24.
- Garcia M, Charvin D, Caboche J (2004) Expanded huntingtin activates the c-Jun terminal kinase/c-Jun pathway prior to aggregate formation in striatal neurons in culture. *Neuroscience* 127: 859-870.
- Gardai SJ, Hildeman DA, Frankel SK, Whitlock BB, Frasch SC, Borregaard N, Marrack P, Bratton DL, Henson PM (2004) Phosphorylation of Bax Ser184 by Akt regulates its activity and apoptosis in neutrophils. *J Biol Chem* 279: 21085-21095.
- Gerfen CR (1992) The neostriatal mosaic: multiple levels of compartmental organization in the basal ganglia. *Annu Rev Neurosci* 15: 285-320.

BIBLIOGRAFÍA

- Ghasemzadeh MB, Sharma S, Surmeier DJ, Eberwine JH, Chesselet MF (1996) Multiplicity of glutamate receptor subunits in single striatal neurons: an RNA amplification study. Mol Pharmacol 49: 852-859.
- Gines S, Seong IS, Fossale E, Ivanova E, Trettel F, Gusella JF, Wheeler VC, Persichetti F, MacDonald ME (2003) Specific progressive cAMP reduction implicates energy deficit in presymptomatic Huntington's disease knock-in mice. Hum Mol Genet 12: 497-508.
- Gines S, Bosch M, Marco S, Gavalda N, Diaz-Hernandez M, Lucas JJ, Canals JM, Alberch J (2006) Reduced expression of the TrkB receptor in Huntington's disease mouse models and in human brain. Eur J Neurosci 23: 649-658.
- Ginovart N, Lundin A, Farde L, Halldin C, Backman L, Swahn CG, Pauli S, Sedvall G (1997) PET study of the pre- and post-synaptic dopaminergic markers for the neurodegenerative process in Huntington's disease. Brain 120 (Pt 3): 503-514.
- Glass M, Dragunow M, Faull RL (2000) The pattern of neurodegeneration in Huntington's disease: a comparative study of cannabinoid, dopamine, adenosine and GABA(A) receptor alterations in the human basal ganglia in Huntington's disease. Neuroscience 97: 505-519.
- Gomez-Santos C, Ferrer I, Reiriz J, Vinals F, Barrachina M, Ambrosio S (2002) MPP+ increases alpha-synuclein expression and ERK/MAP-kinase phosphorylation in human neuroblastoma SH-SY5Y cells. Brain Res 935: 32-39.
- Gong X, Tang X, Wiedmann M, Wang X, Peng J, Zheng D, Blair LA, Marshall J, Mao Z (2003) Cdk5-mediated inhibition of the protective effects of transcription factor MEF2 in neurotoxicity-induced apoptosis. Neuron 38: 33-46.
- Gotoh N, Muroya K, Hattori S, Nakamura S, Chida K, Shibuya M (1995) The SH2 domain of Shc suppresses EGF-induced mitogenesis in a dominant negative manner. Oncogene 11: 2525-2533.
- Gotoh N, Tojo A, Shibuya M (1996) A novel pathway from phosphorylation of tyrosine residues 239/240 of Shc, contributing to suppress apoptosis by IL-3. EMBO J 15: 6197-6204.
- Gotoh N, Toyoda M, Shibuya M (1997) Tyrosine phosphorylation sites at amino acids 239 and 240 of Shc are involved in epidermal growth factor-induced mitogenic signaling that is distinct from Ras/mitogen-activated protein kinase activation. Mol Cell Biol 17: 1824-1831.
- Graham DG, Tiffany SM, Bell WR, Jr., Gutknecht WF (1978) Autoxidation versus covalent binding of quinones as the mechanism of toxicity of dopamine, 6-hydroxydopamine, and related compounds toward C1300 neuroblastoma cells in vitro. Mol Pharmacol 14: 644-653.
- Gratacos E, Perez-Navarro E, Tolosa E, Arenas E, Alberch J (2001) Neuroprotection of striatal neurons against kainate excitotoxicity by neurotrophins and GDNF family members. J Neurochem 78: 1287-1296.
- Grewal SS, York RD, Stork PJ (1999) Extracellular-signal-regulated kinase signalling in neurons. Curr Opin Neurobiol 9: 544-553.
- Gu L, Cui T, Fan C, Zhao H, Zhao C, Lu L, Yang H (2009) Involvement of ERK1/2 signaling pathway in DJ-1-induced neuroprotection against oxidative stress. Biochem Biophys Res Commun 383: 469-474.

- Guise S, Braguer D, Carles G, Delacourte A, Briand C (2001) Hyperphosphorylation of tau is mediated by ERK activation during anticancer drug-induced apoptosis in neuroblastoma cells. *J Neurosci Res* 63: 257-267.
- Gutekunst CA, Li SH, Yi H, Ferrante RJ, Li XJ, Hersch SM (1998) The cellular and subcellular localization of huntingtin-associated protein 1 (HAP1): comparison with huntingtin in rat and human. *J Neurosci* 18: 7674-7686.
- Haj FG, Markova B, Klammer LD, Bohmer FD, Neel BG (2003) Regulation of receptor tyrosine kinase signaling by protein tyrosine phosphatase-1B. *J Biol Chem* 278: 739-744.
- Hall A (1998) Rho GTPases and the actin cytoskeleton. *Science* 279: 509-514.
- Hallows JL, Chen K, DePinho RA, Vincent I (2003) Decreased cyclin-dependent kinase 5 (cdk5) activity is accompanied by redistribution of cdk5 and cytoskeletal proteins and increased cytoskeletal protein phosphorylation in p35 null mice. *J Neurosci* 23: 10633-10644.
- Hamdane M, Sambo AV, Delobel P, Begard S, Violleau A, Delacourte A, Bertrand P, Benavides J, Buee L (2003) Mitotic-like tau phosphorylation by p25-Cdk5 kinase complex. *J Biol Chem* 278: 34026-34034.
- Hamdane M, Bretteville A, Sambo AV, Schindowski K, Begard S, Delacourte A, Bertrand P, Buee L (2005) p25/Cdk5-mediated retinoblastoma phosphorylation is an early event in neuronal cell death. *J Cell Sci* 118: 1291-1298.
- Han SK, Mytilineou C, Cohen G (1996) L-DOPA up-regulates glutathione and protects mesencephalic cultures against oxidative stress. *J Neurochem* 66: 501-510.
- Hanada M, Feng J, Hemmings BA (2004) Structure, regulation and function of PKB/AKT--a major therapeutic target. *Biochim Biophys Acta* 1697: 3-16.
- Hansson O, Petersen A, Leist M, Nicotera P, Castilho RF, Brundin P (1999) Transgenic mice expressing a Huntington's disease mutation are resistant to quinolinic acid-induced striatal excitotoxicity. *Proc Natl Acad Sci U S A* 96: 8727-8732.
- Hansson O, Guatteo E, Mercuri NB, Bernardi G, Li XJ, Castilho RF, Brundin P (2001) Resistance to NMDA toxicity correlates with appearance of nuclear inclusions, behavioural deficits and changes in calcium homeostasis in mice transgenic for exon 1 of the huntington gene. *Eur J Neurosci* 14: 1492-1504.
- Hardingham GE, Fukunaga Y, Bading H (2002) Extrasynaptic NMDARs oppose synaptic NMDARs by triggering CREB shut-off and cell death pathways. *Nat Neurosci* 5: 405-414.
- Hardingham GE, Bading H (2003) The Yin and Yang of NMDA receptor signalling. *Trends Neurosci* 26: 81-89.
- Harjes P, Wanker EE (2003) The hunt for huntingtin function: interaction partners tell many different stories. *Trends Biochem Sci* 28: 425-433.
- He XL, Garcia KC (2004) Structure of nerve growth factor complexed with the shared neurotrophin receptor p75. *Science* 304: 870-875.

BIBLIOGRAFÍA

- Hedreen JC, Peyser CE, Folstein SE, Ross CA (1991) Neuronal loss in layers V and VI of cerebral cortex in Huntington's disease. *Neurosci Lett* 133: 257-261.
- Hellmich MR, Pant HC, Wada E, Battey JF (1992) Neuronal cdc2-like kinase: a cdc2-related protein kinase with predominantly neuronal expression. *Proc Natl Acad Sci U S A* 89: 10867-10871.
- Hempstead BL (2006) Dissecting the diverse actions of pro- and mature neurotrophins. *Curr Alzheimer Res* 3: 19-24.
- Hernandez F, Diaz-Hernandez M, Avila J, Lucas JJ (2004) Testing the ubiquitin-proteasome hypothesis of neurodegeneration in vivo. *Trends Neurosci* 27: 66-69.
- Hickey MA, Reynolds GP, Morton AJ (2002) The role of dopamine in motor symptoms in the R6/2 transgenic mouse model of Huntington's disease. *J Neurochem* 81: 46-59.
- Hodgson JG, Smith DJ, McCutcheon K, Koide HB, Nishiyama K, Dinulos MB, Stevens ME, Bissada N, Nasir J, Kanazawa I, Disteche CM, Rubin EM, Hayden MR (1996) Human huntingtin derived from YAC transgenes compensates for loss of murine huntingtin by rescue of the embryonic lethal phenotype. *Hum Mol Genet* 5: 1875-1885.
- Hollmann M, Heinemann S (1994) Cloned glutamate receptors. *Annu Rev Neurosci* 17: 31-108.
- Holtzman DM, Kilbridge J, Li Y, Cunningham ET, Jr., Lenn NJ, Clary DO, Reichardt LF, Mobley WC (1995) TrkA expression in the CNS: evidence for the existence of several novel NGF-responsive CNS neurons. *J Neurosci* 15: 1567-1576.
- Hoyt KR, Reynolds IJ, Hastings TG (1997) Mechanisms of dopamine-induced cell death in cultured rat forebrain neurons: interactions with and differences from glutamate-induced cell death. *Exp Neurol* 143: 269-281.
- Huang EJ, Reichardt LF (2001) Neurotrophins: roles in neuronal development and function. *Annu Rev Neurosci* 24: 677-736.
- Huang HY, Lin SZ, Kuo JS, Chen WF, Wang MJ (2007) G-CSF protects dopaminergic neurons from 6-OHDA-induced toxicity via the ERK pathway. *Neurobiol Aging* 28: 1258-1269.
- Humbert S, Bryson EA, Cordelieres FP, Connors NC, Datta SR, Finkbeiner S, Greenberg ME, Saudou F (2002) The IGF-1/Akt pathway is neuroprotective in Huntington's disease and involves Huntingtin phosphorylation by Akt. *Dev Cell* 2: 831-837.
- Hunter T (1995) Protein kinases and phosphatases: the yin and yang of protein phosphorylation and signaling. *Cell* 80: 225-236.
- Huntington G (1872) On chorea. *Med Surg Reporter* 26: 302-321.
- Huot P, Levesque M, Parent A (2007) The fate of striatal dopaminergic neurons in Parkinson's disease and Huntington's chorea. *Brain* 130: 222-232.
- Ishiguro K, Takamatsu M, Tomizawa K, Omori A, Takahashi M, Arioka M, Uchida T, Imahori K (1992) Tau protein kinase I converts normal tau protein into A68-like component of paired helical filaments. *J Biol Chem* 267: 10897-10901.

- Jackson DM, Westlind-Danielsson A (1994) Dopamine receptors: molecular biology, biochemistry and behavioural aspects. *Pharmacol Ther* 64: 291-370.
- Jaffe AB, Hall A (2005) Rho GTPases: biochemistry and biology. *Annu Rev Cell Dev Biol* 21: 247-269.
- Jakel RJ, Maragos WF (2000) Neuronal cell death in Huntington's disease: a potential role for dopamine. *Trends Neurosci* 23: 239-245.
- Janssens V, Goris J (2001) Protein phosphatase 2A: a highly regulated family of serine/threonine phosphatases implicated in cell growth and signalling. *Biochem J* 353: 417-439.
- Jiang H, Zhang L, Koubi D, Kuo J, Groc L, Rodriguez AI, Hunter TJ, Tang S, Lazarovici P, Gautam SC, Levine RA (2005) Roles of Ras-Erk in apoptosis of PC12 cells induced by trophic factor withdrawal or oxidative stress. *J Mol Neurosci* 25: 133-140.
- Johnson GL, Lapadat R (2002) Mitogen-activated protein kinase pathways mediated by ERK, JNK, and p38 protein kinases. *Science* 298: 1911-1912.
- Junttila MR, Li SP, Westerman J (2008) Phosphatase-mediated crosstalk between MAPK signaling pathways in the regulation of cell survival. *FASEB J* 22: 954-965.
- Kansy JW, Daubner SC, Nishi A, Sotogaku N, Lloyd MD, Nguyen C, Lu L, Haycock JW, Hope BT, Fitzpatrick PF, Bibb JA (2004) Identification of tyrosine hydroxylase as a physiological substrate for Cdk5. *J Neurochem* 91: 374-384.
- Kaplan DR, Miller FD (1997) Signal transduction by the neurotrophin receptors. *Curr Opin Cell Biol* 9: 213-221.
- Kaplan DR, Miller FD (2000) Neurotrophin signal transduction in the nervous system. *Curr Opin Neurobiol* 10: 381-391.
- Kerkerian L, Dusticier N, Nieoullon A (1987) Modulatory effect of dopamine on high-affinity glutamate uptake in the rat striatum. *J Neurochem* 48: 1301-1306.
- Kesavapany S, Amin N, Zheng YL, Nishihara R, Jaffe H, Sihag R, Gutkind JS, Takahashi S, Kulkarni A, Grant P, Pant HC (2004) p35/cyclin-dependent kinase 5 phosphorylation of ras guanine nucleotide releasing factor 2 (RasGRF2) mediates Rac-dependent Extracellular Signal-regulated kinase 1/2 activity, altering RasGRF2 and microtubule-associated protein 1b distribution in neurons. *J Neurosci* 24: 4421-4431.
- Kim E, Sheng M (2004) PDZ domain proteins of synapses. *Nat Rev Neurosci* 5: 771-781.
- Kim M, Lee HS, Laforet G, McIntyre C, Martin EJ, Chang P, Kim TW, Williams M, Reddy PH, Tagle D, Boyce FM, Won L, Heller A, Aronin N, DiFiglia M (1999) Mutant huntingtin expression in clonal striatal cells: dissociation of inclusion formation and neuronal survival by caspase inhibition. *J Neurosci* 19: 964-973.
- Kim Y, Sung JY, Ceglia I, Lee KW, Ahn JH, Halford JM, Kim AM, Kwak SP, Park JB, Ho RS, Schenck A, Bardoni B, Scott JD, Laird AC, Greengard P (2006) Phosphorylation of WAVE1 regulates actin polymerization and dendritic spine morphology. *Nature* 442: 814-817.

BIBLIOGRAFÍA

- Klawans HC, Paulson GW, Barbeau A (1970) Predictive test for Huntington's chorea. *Lancet* 2: 1185-1186.
- Ko J, Humbert S, Bronson RT, Takahashi S, Kulkarni AB, Li E, Tsai LH (2001) p35 and p39 are essential for cyclin-dependent kinase 5 function during neurodevelopment. *J Neurosci* 21: 6758-6771.
- Kohn AD, Kovacina KS, Roth RA (1995) Insulin stimulates the kinase activity of RAC-PK, a pleckstrin homology domain containing ser/thr kinase. *EMBO J* 14: 4288-4295.
- Kondoh K, Nishida E (2007) Regulation of MAP kinases by MAP kinase phosphatases. *Biochim Biophys Acta* 1773: 1227-1237.
- Krieger C, Hu JH, Pelech S (2003) Aberrant protein kinases and phosphoproteins in amyotrophic lateral sclerosis. *Trends Pharmacol Sci* 24: 535-541.
- Kuida K, Zheng TS, Na S, Kuan C, Yang D, Karasuyama H, Rakic P, Flavell RA (1996) Decreased apoptosis in the brain and premature lethality in CPP32-deficient mice. *Nature* 384: 368-372.
- Kuida K, Haydar TF, Kuan CY, Gu Y, Taya C, Karasuyama H, Su MS, Rakic P, Flavell RA (1998) Reduced apoptosis and cytochrome c-mediated caspase activation in mice lacking caspase 9. *Cell* 94: 325-337.
- Kulich SM, Chu CT (2001) Sustained extracellular signal-regulated kinase activation by 6-hydroxydopamine: implications for Parkinson's disease. *J Neurochem* 77: 1058-1066.
- Lad SP, Peterson DA, Bradshaw RA, Neet KE (2003) Individual and combined effects of TrkA and p75NTR nerve growth factor receptors. A role for the high affinity receptor site. *J Biol Chem* 278: 24808-24817.
- Laforet GA, Sapp E, Chase K, McIntyre C, Boyce FM, Campbell M, Cadigan BA, Warzecki L, Tagle DA, Reddy PH, Cepeda C, Calvert CR, Jokel ES, Klapstein GJ, Ariano MA, Levine MS, DiFiglia M, Aronin N (2001) Changes in cortical and striatal neurons predict behavioral and electrophysiological abnormalities in a transgenic murine model of Huntington's disease. *J Neurosci* 21: 9112-9123.
- Lalioti V, Pulido D, Sandoval IV (2010) Cdk5, the multifunctional surveyor. *Cell Cycle* 9: 284-311.
- Landles C, Bates GP (2004) Huntingtin and the molecular pathogenesis of Huntington's disease. Fourth in molecular medicine review series. *EMBO Rep* 5: 958-963.
- Landwehrmeyer GB, Standaert DG, Testa CM, Penney JB, Jr., Young AB (1995) NMDA receptor subunit mRNA expression by projection neurons and interneurons in rat striatum. *J Neurosci* 15: 5297-5307.
- Lau LF, Seymour PA, Sanner MA, Schachter JB (2002) Cdk5 as a drug target for the treatment of Alzheimer's disease. *J Mol Neurosci* 19: 267-273.

- Le Gall M, Chambard JC, Breitmayer JP, Grall D, Pouyssegur J, Obberghen-Schilling E (2000) The p42/p44 MAP kinase pathway prevents apoptosis induced by anchorage and serum removal. *Mol Biol Cell* 11: 1103-1112.
- Leavitt BR, Wellington CL, Hayden MR (1999) Recent insights into the molecular pathogenesis of Huntington disease. *Semin Neurol* 19: 385-395.
- Leavitt BR, Guttman JA, Hodgson JG, Kimel GH, Singaraja R, Vogl AW, Hayden MR (2001) Wild-type huntingtin reduces the cellular toxicity of mutant huntingtin in vivo. *Am J Hum Genet* 68: 313-324.
- Lee FJ, Xue S, Pei L, Vukusic B, Chery N, Wang Y, Wang YT, Niznik HB, Yu XM, Liu F (2002) Dual regulation of NMDA receptor functions by direct protein-protein interactions with the dopamine D1 receptor. *Cell* 111: 219-230.
- Lee JH, Kim HS, Lee SJ, Kim KT (2007) Stabilization and activation of p53 induced by Cdk5 contributes to neuronal cell death. *J Cell Sci* 120: 2259-2271.
- Lee JH, Jeong MW, Kim W, Choi YH, Kim KT (2008) Cooperative roles of c-Abl and Cdk5 in regulation of p53 in response to oxidative stress. *J Biol Chem* 283: 19826-19835.
- Lee KY, Helbing CC, Choi KS, Johnston RN, Wang JH (1997) Neuronal Cdc2-like kinase (Nclk) binds and phosphorylates the retinoblastoma protein. *J Biol Chem* 272: 5622-5626.
- Lee MS, Kwon YT, Li M, Peng J, Friedlander RM, Tsai LH (2000) Neurotoxicity induces cleavage of p35 to p25 by calpain. *Nature* 405: 360-364.
- Lee MS, Tsai LH (2003) Cdk5: one of the links between senile plaques and neurofibrillary tangles? *J Alzheimers Dis* 5: 127-137.
- Lew J, Beaudette K, Litwin CM, Wang JH (1992) Purification and characterization of a novel proline-directed protein kinase from bovine brain. *J Biol Chem* 267: 13383-13390.
- Lew J, Huang QQ, Qi Z, Winkfein RJ, Aebersold R, Hunt T, Wang JH (1994) A brain-specific activator of cyclin-dependent kinase 5. *Nature* 371: 423-426.
- Li BS, Sun MK, 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 U S A* 98: 12742-12747.
- Li JH, Wang YH, Wolfe BB, Krueger KE, Corsi L, Stocca G, Vicini S (1998) Developmental changes in localization of NMDA receptor subunits in primary cultures of cortical neurons. *Eur J Neurosci* 10: 1704-1715.
- Li SH, Li XJ (2004) Huntingtin-protein interactions and the pathogenesis of Huntington's disease. *Trends Genet* 20: 146-154.
- Lievens JC, Woodman B, Mahal A, Bates GP (2002) Abnormal phosphorylation of synapsin I predicts a neuronal transmission impairment in the R6/2 Huntington's disease transgenic mice. *Mol Cell Neurosci* 20: 638-648.

BIBLIOGRAFÍA

- Lievens JC, Rival T, Iche M, Chneiweiss H, Birman S (2005) Expanded polyglutamine peptides disrupt EGF receptor signaling and glutamate transporter expression in Drosophila. *Hum Mol Genet* 14: 713-724.
- Lilja L, Johansson JU, Gromada J, Mandic SA, Fried G, Berggren PO, Bark C (2004) Cyclin-dependent kinase 5 associated with p39 promotes Munc18-1 phosphorylation and Ca(2+)-dependent exocytosis. *J Biol Chem* 279: 29534-29541.
- Lin H, Lin TY, Juang JL (2007) Abl deregulates Cdk5 kinase activity and subcellular localization in Drosophila neurodegeneration. *Cell Death Differ* 14: 607-615.
- Liu Y, Ding X, Wang D, Deng H, Feng M, Wang M, Yu X, Jiang K, Ward T, Aikhionbare F, Guo Z, Forte JG, Yao X (2007) A mechanism of Munc18b-syntaxin 3-SNAP25 complex assembly in regulated epithelial secretion. *FEBS Lett* 581: 4318-4324.
- Liu YF (1998) Expression of polyglutamine-expanded Huntingtin activates the SEK1-JNK pathway and induces apoptosis in a hippocampal neuronal cell line. *J Biol Chem* 273: 28873-28877.
- Lopez-Pajares V, Kim MM, Yuan ZM (2008) Phosphorylation of MDMX mediated by Akt leads to stabilization and induces 14-3-3 binding. *J Biol Chem* 283: 13707-13713.
- Luo S, Vacher C, Davies JE, Rubinsztein DC (2005) Cdk5 phosphorylation of huntingtin reduces its cleavage by caspases: implications for mutant huntingtin toxicity. *J Cell Biol* 169: 647-656.
- Maccioni RB, Munoz JP, Barbeito L (2001) The molecular bases of Alzheimer's disease and other neurodegenerative disorders. *Arch Med Res* 32: 367-381.
- MacDonald V, Halliday G (2002) Pyramidal cell loss in motor cortices in Huntington's disease. *Neurobiol Dis* 10: 378-386.
- Mangiarini L, Sathasivam K, Seller M, Cozens B, Harper A, Hetherington C, Lawton M, Trottier Y, Lehrach H, Davies SW, Bates GP (1996) Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. *Cell* 87: 493-506.
- Mann DM, Oliver R, Snowden JS (1993) The topographic distribution of brain atrophy in Huntington's disease and progressive supranuclear palsy. *Acta Neuropathol* 85: 553-559.
- Manning G, Whyte DB, Martinez R, Hunter T, Sudarsanam S (2002) The protein kinase complement of the human genome. *Science* 298: 1912-1934.
- Mao Z, Bonni A, Xia F, Nadal-Vicens M, Greenberg ME (1999) Neuronal activity-dependent cell survival mediated by transcription factor MEF2. *Science* 286: 785-790.
- Mapelli M, Musacchio A (2003) The structural perspective on CDK5. *Neurosignals* 12: 164-172.
- Marco S, Canudas AM, Canals JM, Gavalda N, Perez-Navarro E, Alberch J (2002) Excitatory amino acids differentially regulate the expression of GDNF, neurturin, and their receptors in the adult rat striatum. *Exp Neurol* 174: 243-252.

- Marshall CJ (1995) Specificity of receptor tyrosine kinase signaling: transient versus sustained extracellular signal-regulated kinase activation. *Cell* 80: 179-185.
- Marte BM, Downward J (1997) PKB/Akt: connecting phosphoinositide 3-kinase to cell survival and beyond. *Trends Biochem Sci* 22: 355-358.
- Martelli AM, Faenza I, Billi AM, Manzoli L, Evangelisti C, Fala F, Cocco L (2006) Intranuclear 3'-phosphoinositide metabolism and Akt signaling: new mechanisms for tumorigenesis and protection against apoptosis? *Cell Signal* 18: 1101-1107.
- Martin-Aparicio E, Yamamoto A, Hernandez F, Hen R, Avila J, Lucas JJ (2001) Proteasomal-dependent aggregate reversal and absence of cell death in a conditional mouse model of Huntington's disease. *J Neurosci* 21: 8772-8781.
- Martin JB, Gusella JF (1986) Huntington's disease. Pathogenesis and management. *N Engl J Med* 315: 1267-1276.
- Martin TF (1998) Phosphoinositide lipids as signaling molecules: common themes for signal transduction, cytoskeletal regulation, and membrane trafficking. *Annu Rev Cell Dev Biol* 14: 231-264.
- Mattila E, Pellinen T, Nevo J, Vuoriluoto K, Arjonen A, Ivaska J (2005) Negative regulation of EGFR signalling through integrin-alpha1beta1-mediated activation of protein tyrosine phosphatase TCPTP. *Nat Cell Biol* 7: 78-85.
- Maurer U, Charvet C, Wagman AS, Dejardin E, Green DR (2006) Glycogen synthase kinase-3 regulates mitochondrial outer membrane permeabilization and apoptosis by destabilization of MCL-1. *Mol Cell* 21: 749-760.
- Mayo LD, Donner DB (2001) A phosphatidylinositol 3-kinase/Akt pathway promotes translocation of Mdm2 from the cytoplasm to the nucleus. *Proc Natl Acad Sci U S A* 98: 11598-11603.
- McKay MM, Morrison DK (2007) Integrating signals from RTKs to ERK/MAPK. *Oncogene* 26: 3113-3121.
- McLaughlin BA, Nelson D, Erecinska M, Chesselet MF (1998) Toxicity of dopamine to striatal neurons in vitro and potentiation of cell death by a mitochondrial inhibitor. *J Neurochem* 70: 2406-2415.
- Meloche S, Pouyssegur J (2007) The ERK1/2 mitogen-activated protein kinase pathway as a master regulator of the G1- to S-phase transition. *Oncogene* 26: 3227-3239.
- Menalled LB, Sison JD, Dragatsis I, Zeitlin S, Chesselet MF (2003) Time course of early motor and neuropathological anomalies in a knock-in mouse model of Huntington's disease with 140 CAG repeats. *J Comp Neurol* 465: 11-26.
- Merienne K, Helmlinger D, Perkin GR, Devys D, Trottier Y (2003) Polyglutamine expansion induces a protein-damaging stress connecting heat shock protein 70 to the JNK pathway. *J Biol Chem* 278: 16957-16967.

BIBLIOGRAFÍA

- Merlio JP, Ernfors P, Jaber M, Persson H (1992) Molecular cloning of rat trkC and distribution of cells expressing messenger RNAs for members of the trk family in the rat central nervous system. *Neuroscience* 51: 513-532.
- Meyerson M, Enders GH, Wu CL, Su LK, Gorka C, Nelson C, Harlow E, Tsai LH (1992) A family of human cdc2-related protein kinases. *EMBO J* 11: 2909-2917.
- Michaelis ML (2003) Drugs targeting Alzheimer's disease: some things old and some things new. *J Pharmacol Exp Ther* 304: 897-904.
- Migliaccio E, Mele S, Salcini AE, Pelicci G, Lai KM, Superti-Furga G, Pawson T, Di Fiore PP, Lanfrancone L, Pelicci PG (1997) Opposite effects of the p52shc/p46shc and p66shc splicing isoforms on the EGF receptor-MAP kinase-fos signalling pathway. *EMBO J* 16: 706-716.
- Mishra R, Barthwal MK, Sondarva G, Rana B, Wong L, Chatterjee M, Woodgett JR, Rana A (2007) Glycogen synthase kinase-3beta induces neuronal cell death via direct phosphorylation of mixed lineage kinase 3. *J Biol Chem* 282: 30393-30405.
- Mitchell IJ, Cooper AJ, Griffiths MR (1999) The selective vulnerability of striatopallidal neurons. *Prog Neurobiol* 59: 691-719.
- Mitra SK, Hanson DA, Schlaepfer DD (2005) Focal adhesion kinase: in command and control of cell motility. *Nat Rev Mol Cell Biol* 6: 56-68.
- Mitra SK, Schlaepfer DD (2006) Integrin-regulated FAK-Src signaling in normal and cancer cells. *Curr Opin Cell Biol* 18: 516-523.
- Miyamoto Y, Yamauchi J, Tanoue A (2008) Cdk5 phosphorylation of WAVE2 regulates oligodendrocyte precursor cell migration through nonreceptor tyrosine kinase Fyn. *J Neurosci* 28: 8326-8337.
- Morabito MA, Sheng M, Tsai LH (2004) Cyclin-dependent kinase 5 phosphorylates the N-terminal domain of the postsynaptic density protein PSD-95 in neurons. *J Neurosci* 24: 865-876.
- Morgan DO (1995) Principles of CDK regulation. *Nature* 374: 131-134.
- Moser M, Legate KR, Zent R, Fassler R (2009) The tail of integrins, talin, and kindlins. *Science* 324: 895-899.
- Moy LY, Tsai LH (2004) Cyclin-dependent kinase 5 phosphorylates serine 31 of tyrosine hydroxylase and regulates its stability. *J Biol Chem* 279: 54487-54493.
- Murphy M, Dutton R, Koblar S, Cheema S, Bartlett P (1997) Cytokines which signal through the LIF receptor and their actions in the nervous system. *Prog Neurobiol* 52: 355-378.
- Myers RH, Vonsattel JP, Stevens TJ, Cupples LA, Richardson EP, Martin JB, Bird ED (1988) Clinical and neuropathologic assessment of severity in Huntington's disease. *Neurology* 38: 341-347.

- Nakamura S, Kawamoto Y, Nakano S, Ikemoto A, Akiguchi I, Kimura J (1997) Cyclin-dependent kinase 5 in Lewy body-like inclusions in anterior horn cells of a patient with sporadic amyotrophic lateral sclerosis. *Neurology* 48: 267-270.
- Nasir J, Floresco SB, O'Kusky JR, Diewert VM, Richman JM, Zeisler J, Borowski A, Marth JD, Phillips AG, Hayden MR (1995) Targeted disruption of the Huntington's disease gene results in embryonic lethality and behavioral and morphological changes in heterozygotes. *Cell* 81: 811-823.
- Nath R, Davis M, Probert AW, Kupina NC, Ren X, Schielke GP, Wang KK (2000) Processing of cdk5 activator p35 to its truncated form (p25) by calpain in acutely injured neuronal cells. *Biochem Biophys Res Commun* 274: 16-21.
- Naumann T, Casademunt E, Hollerbach E, Hofmann J, Dechant G, Frotscher M, Barde YA (2002) Complete deletion of the neurotrophin receptor p75NTR leads to long-lasting increases in the number of basal forebrain cholinergic neurons. *J Neurosci* 22: 2409-2418.
- Naver B, Stub C, Moller M, Fenger K, Hansen AK, Hasholt L, Sorensen SA (2003) Molecular and behavioral analysis of the R6/1 Huntington's disease transgenic mouse. *Neuroscience* 122: 1049-1057.
- Neri LM, Borgatti P, Capitani S, Martelli AM (2002) The nuclear phosphoinositide 3-kinase/AKT pathway: a new second messenger system. *Biochim Biophys Acta* 1584: 73-80.
- Neystat M, Rzhetskaya M, Oo TF, Kholodilov N, Yarygina O, Wilson A, El Khodor BF, Burke RE (2001) Expression of cyclin-dependent kinase 5 and its activator p35 in models of induced apoptotic death in neurons of the substantia nigra in vivo. *J Neurochem* 77: 1611-1625.
- Nguyen MD, Lariviere RC, Julien JP (2001) Deregulation of Cdk5 in a mouse model of ALS: toxicity alleviated by perikaryal neurofilament inclusions. *Neuron* 30: 135-147.
- Nguyen MD, Mushynski WE, Julien JP (2002) Cycling at the interface between neurodevelopment and neurodegeneration. *Cell Death Differ* 9: 1294-1306.
- Nguyen MD, Julien JP (2003) Cyclin-dependent kinase 5 in amyotrophic lateral sclerosis. *Neurosignals* 12: 215-220.
- Nikolic M, Dudek H, Kwon YT, Ramos YF, Tsai LH (1996) The cdk5/p35 kinase is essential for neurite outgrowth during neuronal differentiation. *Genes Dev* 10: 816-825.
- Nikolic M, Chou MM, Lu W, Mayer BJ, Tsai LH (1998) The p35/Cdk5 kinase is a neuron-specific Rac effector that inhibits Pak1 activity. *Nature* 395: 194-198.
- Nikolic M (2002) The role of Rho GTPases and associated kinases in regulating neurite outgrowth. *Int J Biochem Cell Biol* 34: 731-745.
- Nishitoh H, Saitoh M, Mochida Y, Takeda K, Nakano H, Rothe M, Miyazono K, Ichijo H (1998) ASK1 is essential for JNK/SAPK activation by TRAF2. *Mol Cell* 2: 389-395.
- Nishitoh H, Matsuzawa A, Tobiume K, Saegusa K, Takeda K, Inoue K, Hori S, Kakizuka A, Ichijo H (2002) ASK1 is essential for endoplasmic reticulum stress-induced neuronal cell death triggered by expanded polyglutamine repeats. *Genes Dev* 16: 1345-1355.

BIBLIOGRAFÍA

- Offen D, Ziv I, Sternin H, Melamed E, Hochman A (1996) Prevention of dopamine-induced cell death by thiol antioxidants: possible implications for treatment of Parkinson's disease. *Exp Neurol* 141: 32-39.
- Okada S, Yamauchi K, Pessin JE (1995) Shc isoform-specific tyrosine phosphorylation by the insulin and epidermal growth factor receptors. *J Biol Chem* 270: 20737-20741.
- Okamoto S, Pouladi MA, Talantova M, Yao D, Xia P, Ehrnhoefer DE, Zaidi R, Clemente A, Kaul M, Graham RK, Zhang D, Vincent Chen HS, Tong G, Hayden MR, Lipton SA (2009) Balance between synaptic versus extrasynaptic NMDA receptor activity influences inclusions and neurotoxicity of mutant huntingtin. *Nat Med* 15: 1407-1413.
- Ordway JM, Tallaksen-Greene S, Gutekunst CA, Bernstein EM, Cearley JA, Wiener HW, Dure LS, Lindsey R, Hersch SM, Jope RS, Albin RL, Detloff PJ (1997) Ectopically expressed CAG repeats cause intranuclear inclusions and a progressive late onset neurological phenotype in the mouse. *Cell* 91: 753-763.
- Orlando LR, Ayala R, Kett LR, Curley AA, Duffner J, Bragg DC, Tsai LH, Dunah AW, Young AB (2009) Phosphorylation of the homer-binding domain of group I metabotropic glutamate receptors by cyclin-dependent kinase 5. *J Neurochem* 110: 557-569.
- Ortega Z, Diaz-Hernandez M, Maynard CJ, Hernandez F, Dantuma NP, Lucas JJ (2010) Acute polyglutamine expression in inducible mouse model unravels ubiquitin/proteasome system impairment and permanent recovery attributable to aggregate formation. *J Neurosci* 30: 3675-3688.
- Owens DM, Keyse SM (2007) Differential regulation of MAP kinase signalling by dual-specificity protein phosphatases. *Oncogene* 26: 3203-3213.
- Oyanagi K, Takeda S, Takahashi H, Ohama E, Ikuta F (1989) A quantitative investigation of the substantia nigra in Huntington's disease. *Ann Neurol* 26: 13-19.
- Ozes ON, Mayo LD, Gustin JA, Pfeffer SR, Pfeffer LM, Donner DB (1999) NF-kappaB activation by tumour necrosis factor requires the Akt serine-threonine kinase. *Nature* 401: 82-85.
- Paglini G, Peris L, Diez-Guerra J, Quiroga S, Caceres A (2001) The Cdk5-p35 kinase associates with the Golgi apparatus and regulates membrane traffic. *EMBO Rep* 2: 1139-1144.
- Pandithage R, Lilischkis R, Harting K, Wolf A, Jedamzik B, Luscher-Firzlaff J, Vervoorts J, Lasonder E, Kremmer E, Knoll B, Luscher B (2008) The regulation of SIRT2 function by cyclin-dependent kinases affects cell motility. *J Cell Biol* 180: 915-929.
- Pap M, Cooper GM (1998) Role of glycogen synthase kinase-3 in the phosphatidylinositol 3-Kinase/Akt cell survival pathway. *J Biol Chem* 273: 19929-19932.
- Pardo R, Colin E, Regulier E, Aebischer P, Deglon N, Humbert S, Saudou F (2006) Inhibition of calcineurin by FK506 protects against polyglutamine-huntingtin toxicity through an increase of huntingtin phosphorylation at S421. *J Neurosci* 26: 1635-1645.
- Patrick GN, Zhou P, Kwon YT, Howley PM, Tsai LH (1998) p35, the neuronal-specific activator of cyclin-dependent kinase 5 (Cdk5) is degraded by the ubiquitin-proteasome pathway. *J Biol Chem* 273: 24057-24064.

- Patrick GN, Zukerberg L, Nikolic M, de la MS, Dikkes P, Tsai LH (1999) Conversion of p35 to p25 deregulates Cdk5 activity and promotes neurodegeneration. *Nature* 402: 615-622.
- Patzke H, Tsai LH (2002) Calpain-mediated cleavage of the cyclin-dependent kinase-5 activator p39 to p29. *J Biol Chem* 277: 8054-8060.
- Paul S, Nairn AC, Wang P, Lombroso PJ (2003) NMDA-mediated activation of the tyrosine phosphatase STEP regulates the duration of ERK signaling. *Nat Neurosci* 6: 34-42.
- Payrastre B, Missy K, Giuriato S, Bodin S, Plantavid M, Gratacap M (2001) Phosphoinositides: key players in cell signalling, in time and space. *Cell Signal* 13: 377-387.
- Pearson G, Robinson F, Beers GT, Xu BE, Karandikar M, Berman K, Cobb MH (2001) Mitogen-activated protein (MAP) kinase pathways: regulation and physiological functions. *Endocr Rev* 22: 153-183.
- Pei JJ, Braak H, An WL, Winblad B, Cowburn RF, Iqbal K, Grundke-Iqbali I (2002) Up-regulation of mitogen-activated protein kinases ERK1/2 and MEK1/2 is associated with the progression of neurofibrillary degeneration in Alzheimer's disease. *Brain Res Mol Brain Res* 109: 45-55.
- Pei L, Lee FJ, Moszczynska A, Vukusic B, Liu F (2004) Regulation of dopamine D1 receptor function by physical interaction with the NMDA receptors. *J Neurosci* 24: 1149-1158.
- Peng TI, Greenamyre JT (1998) Privileged access to mitochondria of calcium influx through N-methyl-D-aspartate receptors. *Mol Pharmacol* 53: 974-980.
- Perez-Navarro E, Alberch J, Neveu I, Arenas E (1999) Brain-derived neurotrophic factor, neurotrophin-3 and neurotrophin-4/5 differentially regulate the phenotype and prevent degenerative changes in striatal projection neurons after excitotoxicity in vivo. *Neuroscience* 91: 1257-1264.
- Perez-Navarro E, Canudas AM, Akerund P, Alberch J, Arenas E (2000) Brain-derived neurotrophic factor, neurotrophin-3, and neurotrophin-4/5 prevent the death of striatal projection neurons in a rodent model of Huntington's disease. *J Neurochem* 75: 2190-2199.
- Perez-Navarro E, Gavalda N, Gratacos E, Alberch J (2005) Brain-derived neurotrophic factor prevents changes in Bcl-2 family members and caspase-3 activation induced by excitotoxicity in the striatum. *J Neurochem* 92: 678-691.
- Perez-Navarro E, Canals JM, Gines S, Alberch J (2006) Cellular and molecular mechanisms involved in the selective vulnerability of striatal projection neurons in Huntington's disease. *Histol Histopathol* 21: 1217-1232.
- Perry G, Roder H, Nunomura A, Takeda A, Friedlich AL, Zhu X, Raina AK, Holbrook N, Siedlak SL, Harris PL, Smith MA (1999) Activation of neuronal extracellular receptor kinase (ERK) in Alzheimer disease links oxidative stress to abnormal phosphorylation. *Neuroreport* 10: 2411-2415.
- Persad S, Attwell S, Gray V, Mawji N, Deng JT, Leung D, Yan J, Sanghera J, Walsh MP, Dedhar S (2001) Regulation of protein kinase B/Akt-serine 473 phosphorylation by integrin-linked kinase: critical roles for kinase activity and amino acids arginine 211 and serine 343. *J Biol Chem* 276: 27462-27469.

BIBLIOGRAFÍA

- Petersen A, Chase K, Puschban Z, DiFiglia M, Brundin P, Aronin N (2002) Maintenance of susceptibility to neurodegeneration following intrastriatal injections of quinolinic acid in a new transgenic mouse model of Huntington's disease. *Exp Neurol* 175: 297-300.
- Pineda JR, Canals JM, Bosch M, Adell A, Mengod G, Artigas F, Ernfors P, Alberch J (2005) Brain-derived neurotrophic factor modulates dopaminergic deficits in a transgenic mouse model of Huntington's disease. *J Neurochem* 93: 1057-1068.
- Poon RY, Lew J, Hunter T (1997) Identification of functional domains in the neuronal Cdk5 activator protein. *J Biol Chem* 272: 5703-5708.
- Przedborski S (2007) Peroxiredoxin-2 links Cdk5 to neurodegeneration. *Nat Med* 13: 907-909.
- Qi Z, Huang QQ, Lee KY, Lew J, Wang JH (1995) Reconstitution of neuronal Cdc2-like kinase from bacteria-expressed Cdk5 and an active fragment of the brain-specific activator. Kinase activation in the absence of Cdk5 phosphorylation. *J Biol Chem* 270: 10847-10854.
- Raman M, Chen W, Cobb MH (2007) Differential regulation and properties of MAPKs. *Oncogene* 26: 3100-3112.
- Ramos JW (2008) The regulation of extracellular signal-regulated kinase (ERK) in mammalian cells. *Int J Biochem Cell Biol* 40: 2707-2719.
- Rashid T, Banerjee M, Nikolic M (2001) Phosphorylation of Pak1 by the p35/Cdk5 kinase affects neuronal morphology. *J Biol Chem* 276: 49043-49052.
- Ravichandran KS (2001) Signaling via Shc family adapter proteins. *Oncogene* 20: 6322-6330.
- Ravikumar B, Vacher C, Berger Z, Davies JE, Luo S, Oroz LG, Scaravilli F, Easton DF, Duden R, O'Kane CJ, Rubinsztein DC (2004) Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. *Nat Genet* 36: 585-595.
- Reddy PH, Williams M, Charles V, Garrett L, Pike-Buchanan L, Whetsell WO, Jr., Miller G, Tagle DA (1998) Behavioural abnormalities and selective neuronal loss in HD transgenic mice expressing mutated full-length HD cDNA. *Nat Genet* 20: 198-202.
- Reichardt LF (2006) Neurotrophin-regulated signalling pathways. *Philos Trans R Soc Lond B Biol Sci* 361: 1545-1564.
- Reiner A, Albin RL, Anderson KD, D'Amato CJ, Penney JB, Young AB (1988) Differential loss of striatal projection neurons in Huntington disease. *Proc Natl Acad Sci U S A* 85: 5733-5737.
- Reynolds GP, Dalton CF, Tillery CL, Mangiarini L, Davies SW, Bates GP (1999) Brain neurotransmitter deficits in mice transgenic for the Huntington's disease mutation. *J Neurochem* 72: 1773-1776.
- Reynolds IJ, Hastings TG (1995) Glutamate induces the production of reactive oxygen species in cultured forebrain neurons following NMDA receptor activation. *J Neurosci* 15: 3318-3327.

- Richfield EK, Maguire-Zeiss KA, Vonkeman HE, Voorn P (1995) Preferential loss of preproenkephalin versus preprotachykinin neurons from the striatum of Huntington's disease patients. *Ann Neurol* 38: 852-861.
- Rigamonti D, Bauer JH, De Fraja C, Conti L, Sipione S, Sciorati C, Clementi E, Hackam A, Hayden MR, Li Y, Cooper JK, Ross CA, Govoni S, Vincenz C, Cattaneo E (2000) Wild-type huntingtin protects from apoptosis upstream of caspase-3. *J Neurosci* 20: 3705-3713.
- Rigamonti D, Sipione S, Goffredo D, Zuccato C, Fossale E, Cattaneo E (2001) Huntington's neuroprotective activity occurs via inhibition of procaspase-9 processing. *J Biol Chem* 276: 14545-14548.
- Romashkova JA, Makarov SS (1999) NF-kappaB is a target of AKT in anti-apoptotic PDGF signalling. *Nature* 401: 86-90.
- Rosenberg PA (1988) Catecholamine toxicity in cerebral cortex in dissociated cell culture. *J Neurosci* 8: 2887-2894.
- Ross CA, Poirier MA (2004) Protein aggregation and neurodegenerative disease. *Nat Med* 10 Suppl: S10-S17.
- Ross CA, Pickart CM (2004) The ubiquitin-proteasome pathway in Parkinson's disease and other neurodegenerative diseases. *Trends Cell Biol* 14: 703-711.
- Ross CA, Poirier MA (2005) Opinion: What is the role of protein aggregation in neurodegeneration? *Nat Rev Mol Cell Biol* 6: 891-898.
- 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.
- Rubinfeld H, Seger R (2005) The ERK cascade: a prototype of MAPK signaling. *Mol Biotechnol* 31: 151-174.
- Rubio I, Rennert K, Wittig U, Beer K, Durst M, Stang SL, Stone J, Wetzker R (2006) Ras activation in response to phorbol ester proceeds independently of the EGFR via an unconventional nucleotide-exchange factor system in COS-7 cells. *Biochem J* 398: 243-256.
- Ryan AB, Zeitlin SO, Scoble H (2006) Genetic interaction between expanded murine Hdh alleles and p53 reveal deleterious effects of p53 on Huntington's disease pathogenesis. *Neurobiol Dis* 24: 419-427.
- Saavedra A, Garcia-Martinez JM, Xifro X, Giralt A, Torres-Peraza JF, Canals JM, Diaz-Hernandez M, Lucas JJ, Alberch J, Perez-Navarro E (2010) PH domain leucine-rich repeat protein phosphatase 1 contributes to maintain the activation of the PI3K/Akt pro-survival pathway in Huntington's disease striatum. *Cell Death Differ* 17: 324-335.
- Sanchez AM, Flamini MI, Fu XD, Mannella P, Giretti MS, Goglia L, Genazzani AR, Simoncini T (2009) Rapid signaling of estrogen to WAVE1 and moesin controls neuronal spine formation via the actin cytoskeleton. *Mol Endocrinol* 23: 1193-1202.

BIBLIOGRAFÍA

- Sano I, Gamo T, Kakimoto Y, Taniguchi K, Takesada M, Nishinuma K (1959) Distribution of catechol compounds in human brain. *Biochim Biophys Acta* 32: 586-587.
- Sarbassov DD, Guertin DA, Ali SM, Sabatini DM (2005) Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. *Science* 307: 1098-1101.
- Sasaki Y, Cheng C, Uchida Y, Nakajima O, Ohshima T, Yagi T, Taniguchi M, Nakayama T, Kishida R, Kudo Y, Ohno S, Nakamura F, Goshima Y (2002) Fyn and Cdk5 mediate semaphorin-3A signaling, which is involved in regulation of dendrite orientation in cerebral cortex. *Neuron* 35: 907-920.
- Saudou F, Finkbeiner S, Devys D, Greenberg ME (1998) Huntingtin acts in the nucleus to induce apoptosis but death does not correlate with the formation of intranuclear inclusions. *Cell* 95: 55-66.
- Scheid MP, Lauener RW, Duronio V (1995) Role of phosphatidylinositol 3-OH-kinase activity in the inhibition of apoptosis in haemopoietic cells: phosphatidylinositol 3-OH-kinase inhibitors reveal a difference in signalling between interleukin-3 and granulocyte-macrophage colony stimulating factor. *Biochem J* 312 (Pt 1): 159-162.
- Schilling B, Gafni J, Torcassi C, Cong X, Row RH, LaFevre-Bernt MA, Cusack MP, Ratovitski T, Hirschhorn R, Ross CA, Gibson BW, Ellerby LM (2006) Huntingtin phosphorylation sites mapped by mass spectrometry. Modulation of cleavage and toxicity. *J Biol Chem* 281: 23686-23697.
- Schilling G, Becher MW, Sharp AH, Jinnah HA, Duan K, Kotzuk JA, Slunt HH, Ratovitski T, Cooper JK, Jenkins NA, Copeland NG, Price DL, Ross CA, Borchelt DR (1999) Intranuclear inclusions and neuritic aggregates in transgenic mice expressing a mutant N-terminal fragment of huntingtin. *Hum Mol Genet* 8: 397-407.
- Schoepfer R, Monyer H, Sommer B, Wisden W, Sprengel R, Kuner T, Lomeli H, Herb A, Kohler M, Burnashev N (1994) Molecular biology of glutamate receptors. *Prog Neurobiol* 42: 353-357.
- Schwarz R, Kohler C (1983) Differential vulnerability of central neurons of the rat to quinolinic acid. *Neurosci Lett* 38: 85-90.
- Scott L, Kruse MS, Forssberg H, Brismar H, Greengard P, Aperia A (2002) Selective up-regulation of dopamine D1 receptors in dendritic spines by NMDA receptor activation. *Proc Natl Acad Sci U S A* 99: 1661-1664.
- Scott L, Zelenin S, Malmersjo S, Kowalewski JM, Markus EZ, Nairn AC, Greengard P, Brismar H, Aperia A (2006) Allosteric changes of the NMDA receptor trap diffusible dopamine 1 receptors in spines. *Proc Natl Acad Sci U S A* 103: 762-767.
- Scott L, Aperia A (2009) Interaction between N-methyl-D-aspartic acid receptors and D1 dopamine receptors: an important mechanism for brain plasticity. *Neuroscience* 158: 62-66.
- Seong IS, Ivanova E, Lee JM, Choo YS, Fossale E, Anderson M, Gusella JF, Laramie JM, Myers RH, Lesort M, MacDonald ME (2005) HD CAG repeat implicates a dominant property of huntingtin in mitochondrial energy metabolism. *Hum Mol Genet* 14: 2871-2880.

- Shahani N, Subramaniam S, Wolf T, Tackenberg C, Brandt R (2006) Tau aggregation and progressive neuronal degeneration in the absence of changes in spine density and morphology after targeted expression of Alzheimer's disease-relevant tau constructs in organotypic hippocampal slices. *J Neurosci* 26: 6103-6114.
- Sharma P, Sharma M, Amin ND, Albers RW, Pant HC (1999) Regulation of cyclin-dependent kinase 5 catalytic activity by phosphorylation. *Proc Natl Acad Sci U S A* 96: 11156-11160.
- Shea TB, Yabe JT, Ortiz D, Pimenta A, Loomis P, Goldman RD, Amin N, Pant HC (2004) Cdk5 regulates axonal transport and phosphorylation of neurofilaments in cultured neurons. *J Cell Sci* 117: 933-941.
- Shehadeh J, Fernandes HB, Zeron Mullins MM, Graham RK, Leavitt BR, Hayden MR, Raymond LA (2006) Striatal neuronal apoptosis is preferentially enhanced by NMDA receptor activation in YAC transgenic mouse model of Huntington disease. *Neurobiol Dis* 21: 392-403.
- Shelton SB, Johnson GV (2004) Cyclin-dependent kinase-5 in neurodegeneration. *J Neurochem* 88: 1313-1326.
- Shetty KT, Link WT, Pant HC (1993) cdc2-like kinase from rat spinal cord specifically phosphorylates KSPXK motifs in neurofilament proteins: isolation and characterization. *Proc Natl Acad Sci U S A* 90: 6844-6848.
- Silverstein AM, Barrow CA, Davis AJ, Mumby MC (2002) Actions of PP2A on the MAP kinase pathway and apoptosis are mediated by distinct regulatory subunits. *Proc Natl Acad Sci U S A* 99: 4221-4226.
- Smith DS, Greer PL, Tsai LH (2001) Cdk5 on the brain. *Cell Growth Differ* 12: 277-283.
- Smith PD, Crocker SJ, Jackson-Lewis V, Jordan-Sciutto KL, Hayley S, Mount MP, O'Hare MJ, Callaghan S, Slack RS, Przedborski S, Anisman H, Park DS (2003) Cyclin-dependent kinase 5 is a mediator of dopaminergic neuron loss in a mouse model of Parkinson's disease. *Proc Natl Acad Sci U S A* 100: 13650-13655.
- Smith PD, Mount MP, Shree R, Callaghan S, Slack RS, Anisman H, Vincent I, Wang X, Mao Z, Park DS (2006) Calpain-regulated p35/cdk5 plays a central role in dopaminergic neuron death through modulation of the transcription factor myocyte enhancer factor 2. *J Neurosci* 26: 440-447.
- Snyder GL, Fienberg AA, Huganir RL, Greengard P (1998) A dopamine/D1 receptor/protein kinase A/dopamine- and cAMP-regulated phosphoprotein (Mr 32 kDa)/protein phosphatase-1 pathway regulates dephosphorylation of the NMDA receptor. *J Neurosci* 18: 10297-10303.
- Sole C, Dolcet X, Segura MF, Gutierrez H, Diaz-Meco MT, Gozzelino R, Sanchis D, Bayascas JR, Gallego C, Moscat J, Davies AM, Comella JX (2004) The death receptor antagonist FAIM promotes neurite outgrowth by a mechanism that depends on ERK and NF-kapp B signaling. *J Cell Biol* 167: 479-492.
- Sonenshein GE (1997) Rel/NF-kappa B transcription factors and the control of apoptosis. *Semin Cancer Biol* 8: 113-119.

BIBLIOGRAFÍA

- Song C, Perides G, Liu YF (2002) Expression of full-length polyglutamine-expanded Huntingtin disrupts growth factor receptor signaling in rat pheochromocytoma (PC12) cells. *J Biol Chem* 277: 6703-6707.
- Song C, Zhang Y, Parsons CG, Liu YF (2003) Expression of polyglutamine-expanded huntingtin induces tyrosine phosphorylation of N-methyl-D-aspartate receptors. *J Biol Chem* 278: 33364-33369.
- Soriano FX, Papadia S, Hofmann F, Hardingham NR, Bading H, Hardingham GE (2006) Preconditioning doses of NMDA promote neuroprotection by enhancing neuronal excitability. *J Neurosci* 26: 4509-4518.
- Sotrel A, Paskevich PA, Kiely DK, Bird ED, Williams RS, Myers RH (1991) Morphometric analysis of the prefrontal cortex in Huntington's disease. *Neurology* 41: 1117-1123.
- Sourkes TL (1976) Parkinson's disease and other disorders of the basal ganglia. In basic Neurochemistry (Siegel GJ et al., eds) pp 668-684. Little, Brown & Company.
- Spina MB, Cohen G (1988) Exposure of striatal [corrected] synaptosomes to L-dopa increases levels of oxidized glutathione. *J Pharmacol Exp Ther* 247: 502-507.
- Stack EC, Kubilus JK, Smith K, Cormier K, Del Signore SJ, Guelin E, Ryu H, Hersch SM, Ferrante RJ (2005) Chronology of behavioral symptoms and neuropathological sequela in R6/2 Huntington's disease transgenic mice. *J Comp Neurol* 490: 354-370.
- Standaert DG, Testa CM, Young AB, Penney JB, Jr. (1994) Organization of N-methyl-D-aspartate glutamate receptor gene expression in the basal ganglia of the rat. *J Comp Neurol* 343: 1-16.
- Strohmaier C, Carter BD, Urfer R, Barde YA, Dechant G (1996) A splice variant of the neurotrophin receptor trkB with increased specificity for brain-derived neurotrophic factor. *EMBO J* 15: 3332-3337.
- Strong TV, Tagle DA, Valdes JM, Elmer LW, Boehm K, Swaroop M, Kaatz KW, Collins FS, Albin RL (1993) Widespread expression of the human and rat Huntington's disease gene in brain and nonneuronal tissues. *Nat Genet* 5: 259-265.
- Subramaniam S, Unsicker K (2010) ERK and cell death: ERK1/2 in neuronal death. *FEBS J* 277: 22-29.
- Sulzer D, Zecca L (2000) Intraneuronal dopamine-quinone synthesis: a review. *Neurotox Res* 1: 181-195.
- Sun Y, Savanenin A, Reddy PH, Liu YF (2001) Polyglutamine-expanded huntingtin promotes sensitization of N-methyl-D-aspartate receptors via post-synaptic density 95. *J Biol Chem* 276: 24713-24718.
- Suzuki M, Desmond TJ, Albin RL, Frey KA (2001) Vesicular neurotransmitter transporters in Huntington's disease: initial observations and comparison with traditional synaptic markers. *Synapse* 41: 329-336.

- Takahashi K, Hamada N, Yamamoto D (2002) Ras target protein canoe is a substrate for Cdc2 and Cdk5 kinases. *Arch Insect Biochem Physiol* 49: 102-107.
- Tamguney T, Stokoe D (2007) New insights into PTEN. *J Cell Sci* 120: 4071-4079.
- Tanaka T, Serneo FF, Tseng HC, Kulkarni AB, Tsai LH, Gleeson JG (2004) Cdk5 phosphorylation of doublecortin ser297 regulates its effect on neuronal migration. *Neuron* 41: 215-227.
- Tang D, Yeung J, Lee KY, Matsushita M, Matsui H, Tomizawa K, Hatase O, Wang JH (1995) An isoform of the neuronal cyclin-dependent kinase 5 (Cdk5) activator. *J Biol Chem* 270: 26897-26903.
- Tang ED, Nunez G, Barr FG, Guan KL (1999) Negative regulation of the forkhead transcription factor FKHR by Akt. *J Biol Chem* 274: 16741-16746.
- Tang TS, Tu H, Chan EY, Maximov A, Wang Z, Wellington CL, Hayden MR, Bezprozvanny I (2003) Huntingtin and huntingtin-associated protein 1 influence neuronal calcium signaling mediated by inositol-(1,4,5) triphosphate receptor type 1. *Neuron* 39: 227-239.
- Tang TS, Slow E, Lupu V, Stavrovskaya IG, Sugimori M, Llinas R, Kristal BS, Hayden MR, Bezprozvanny I (2005) Disturbed Ca²⁺ signaling and apoptosis of medium spiny neurons in Huntington's disease. *Proc Natl Acad Sci U S A* 102: 2602-2607.
- Tang TS, Chen X, Liu J, Bezprozvanny I (2007) Dopaminergic signaling and striatal neurodegeneration in Huntington's disease. *J Neurosci* 27: 7899-7910.
- Tang X, Wang X, Gong X, Tong M, Park D, Xia Z, Mao Z (2005) Cyclin-dependent kinase 5 mediates neurotoxin-induced degradation of the transcription factor myocyte enhancer factor 2. *J Neurosci* 25: 4823-4834.
- The Huntington's disease collaborative research group (1993) A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. *Cell* 72: 971-983.
- Thoenen H, Sendtner M (2002) Neurotrophins: from enthusiastic expectations through sobering experiences to rational therapeutic approaches. *Nat Neurosci* 5 Suppl: 1046-1050.
- Toker A, Newton AC (2000) Akt/protein kinase B is regulated by autophosphorylation at the hypothetical PDK-2 site. *J Biol Chem* 275: 8271-8274.
- Toledano-Katchalski H, Kraut J, Sines T, Granot-Attas S, Shohat G, Gil-Henn H, Yung Y, Elson A (2003) Protein tyrosine phosphatase epsilon inhibits signaling by mitogen-activated protein kinases. *Mol Cancer Res* 1: 541-550.
- Torres-Peraza JF, Giralt A, Garcia-Martinez JM, Pedrosa E, Canals JM, Alberch J (2008) Disruption of striatal glutamatergic transmission induced by mutant huntingtin involves remodeling of both postsynaptic density and NMDA receptor signaling. *Neurobiol Dis* 29: 409-421.
- Tovar KR, Westbrook GL (1999) The incorporation of NMDA receptors with a distinct subunit composition at nascent hippocampal synapses in vitro. *J Neurosci* 19: 4180-4188.

BIBLIOGRAFÍA

- Trettel F, Rigamonti D, Hilditch-Maguire P, Wheeler VC, Sharp AH, Persichetti F, Cattaneo E, MacDonald ME (2000) Dominant phenotypes produced by the HD mutation in STHdh(Q111) striatal cells. *Hum Mol Genet* 9: 2799-2809.
- Tsai LH, Takahashi T, Caviness VS, Jr., Harlow E (1993) Activity and expression pattern of cyclin-dependent kinase 5 in the embryonic mouse nervous system. *Development* 119: 1029-1040.
- Uchida T, Ishiguro K, Ohnuma J, Takamatsu M, Yonekura S, Imahori K (1994) Precursor of cdk5 activator, the 23 kDa subunit of tau protein kinase II: its sequence and developmental change in brain. *FEBS Lett* 355: 35-40.
- Ugi S, Imamura T, Ricketts W, Olefsky JM (2002) Protein phosphatase 2A forms a molecular complex with Shc and regulates Shc tyrosine phosphorylation and downstream mitogenic signaling. *Mol Cell Biol* 22: 2375-2387.
- Van den Heuvel S, Harlow E (1993) Distinct roles for cyclin-dependent kinases in cell cycle control. *Science* 262: 2050-2054.
- Van Kanegan MJ, Adams DG, Wadzinski BE, Strack S (2005) Distinct protein phosphatase 2A heterotrimers modulate growth factor signaling to extracellular signal-regulated kinases and Akt. *J Biol Chem* 280: 36029-36036.
- Van Raamsdonk JM, Murphy Z, Slow EJ, Leavitt BR, Hayden MR (2005) Selective degeneration and nuclear localization of mutant huntingtin in the YAC128 mouse model of Huntington disease. *Hum Mol Genet* 14: 3823-3835.
- Van Raamsdonk JM, Warby SC, Hayden MR (2007) Selective degeneration in YAC mouse models of Huntington disease. *Brain Res Bull* 72: 124-131.
- Van Weeren PC, de Bruyn KM, Vries-Smits AM, van Lint J, Burgering BM (1998) Essential role for protein kinase B (PKB) in insulin-induced glycogen synthase kinase 3 inactivation. Characterization of dominant-negative mutant of PKB. *J Biol Chem* 273: 13150-13156.
- Vanhaesebroeck B, Waterfield MD (1999) Signaling by distinct classes of phosphoinositide 3-kinases. *Exp Cell Res* 253: 239-254.
- Vanhaesebroeck B, Leevers SJ, Ahmadi K, Timms J, Katso R, Driscoll PC, Woscholski R, Parker PJ, Waterfield MD (2001) Synthesis and function of 3-phosphorylated inositol lipids. *Annu Rev Biochem* 70: 535-602.
- Venkatraman P, Wetzel R, Tanaka M, Nukina N, Goldberg AL (2004) Eukaryotic proteasomes cannot digest polyglutamine sequences and release them during degradation of polyglutamine-containing proteins. *Mol Cell* 14: 95-104.
- Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson EP, Jr. (1985) Neuropathological classification of Huntington's disease. *J Neuropathol Exp Neurol* 44: 559-577.
- Vonsattel JP, DiFiglia M (1998) Huntington disease. *J Neuropathol Exp Neurol* 57: 369-384.

- Wada T, Penninger JM (2004) Mitogen-activated protein kinases in apoptosis regulation. *Oncogene* 23: 2838-2849.
- Wagster MV, Hedreen JC, Peyser CE, Folstein SE, Ross CA (1994) Selective loss of [³H]kainic acid and [³H]AMPA binding in layer VI of frontal cortex in Huntington's disease. *Exp Neurol* 127: 70-75.
- Wang J, Liu S, Fu Y, Wang JH, Lu Y (2003) Cdk5 activation induces hippocampal CA1 cell death by directly phosphorylating NMDA receptors. *Nat Neurosci* 6: 1039-1047.
- Warby SC, Chan EY, Metzler M, Gan L, Singaraja RR, Crocker SF, Robertson HA, Hayden MR (2005) Huntingtin phosphorylation on serine 421 is significantly reduced in the striatum and by polyglutamine expansion in vivo. *Hum Mol Genet* 14: 1569-1577.
- Weeks RA, Piccini P, Harding AE, Brooks DJ (1996) Striatal D1 and D2 dopamine receptor loss in asymptomatic mutation carriers of Huntington's disease. *Ann Neurol* 40: 49-54.
- Weishaupt JH, Neusch C, Bahr M (2003) Cyclin-dependent kinase 5 (CDK5) and neuronal cell death. *Cell Tissue Res* 312: 1-8.
- Wellbrock C, Karasarides M, Marais R (2004) The RAF proteins take centre stage. *Nat Rev Mol Cell Biol* 5: 875-885.
- Wen Z, Zhong Z, Darnell JE, Jr. (1995) Maximal activation of transcription by Stat1 and Stat3 requires both tyrosine and serine phosphorylation. *Cell* 82: 241-250.
- Weston CR, Lambright DG, Davis RJ (2002) Signal transduction. MAP kinase signaling specificity. *Science* 296: 2345-2347.
- Weston CR, Davis RJ (2007) The JNK signal transduction pathway. *Curr Opin Cell Biol* 19: 142-149.
- Wheeler D, Boutelle MG, Fillenz M (1995) The role of N-methyl-D-aspartate receptors in the regulation of physiologically released dopamine. *Neuroscience* 65: 767-774.
- Wheeler VC, White JK, Gutekunst CA, Vrbanac V, Weaver M, Li XJ, Li SH, Yi H, Vonsattel JP, Gusella JF, Hersch S, Auerbach W, Joyner AL, MacDonald ME (2000) Long glutamine tracts cause nuclear localization of a novel form of huntingtin in medium spiny striatal neurons in HdhQ92 and HdhQ111 knock-in mice. *Hum Mol Genet* 9: 503-513.
- Wheeler VC, Gutekunst CA, Vrbanac V, Lebel LA, Schilling G, Hersch S, Friedlander RM, Gusella JF, Vonsattel JP, Borchelt DR, MacDonald ME (2002) Early phenotypes that presage late-onset neurodegenerative disease allow testing of modifiers in Hdh CAG knock-in mice. *Hum Mol Genet* 11: 633-640.
- White JK, Auerbach W, Duyao MP, Vonsattel JP, Gusella JF, Joyner AL, MacDonald ME (1997) Huntingtin is required for neurogenesis and is not impaired by the Huntington's disease CAG expansion. *Nat Genet* 17: 404-410.
- Wu ZL, O'Kane TM, Scott RW, Savage MJ, Bozyczko-Coyne D (2002) Protein tyrosine phosphatases are up-regulated and participate in cell death induced by polyglutamine expansion. *J Biol Chem* 277: 44208-44213.

BIBLIOGRAFÍA

- Xia Z, Dickens M, Raingeaud J, Davis RJ, Greenberg ME (1995) Opposing effects of ERK and JNK-p38 MAP kinases on apoptosis. *Science* 270: 1326-1331.
- Xifro X, Garcia-Martinez JM, Del Toro D, Alberch J, Perez-Navarro E (2008) Calcineurin is involved in the early activation of NMDA-mediated cell death in mutant huntingtin knock-in striatal cells. *J Neurochem* 105: 1596-1612.
- Xifro X, Giralt A, Saavedra A, Garcia-Martinez JM, Diaz-Hernandez M, Lucas JJ, Alberch J, Perez-Navarro E (2009) Reduced calcineurin protein levels and activity in exon-1 mouse models of Huntington's disease: role in excitotoxicity. *Neurobiol Dis* 36: 461-469.
- Xin M, Gao F, May WS, Flagg T, Deng X (2007) Protein kinase Czeta abrogates the proapoptotic function of Bax through phosphorylation. *J Biol Chem* 282: 21268-21277.
- Yamada M, Ohnishi H, Sano S, Nakatani A, Ikeuchi T, Hatanaka H (1997) Insulin receptor substrate (IRS)-1 and IRS-2 are tyrosine-phosphorylated and associated with phosphatidylinositol 3-kinase in response to brain-derived neurotrophic factor in cultured cerebral cortical neurons. *J Biol Chem* 272: 30334-30339.
- Yamamoto A, Lucas JJ, Hen R (2000) Reversal of neuropathology and motor dysfunction in a conditional model of Huntington's disease. *Cell* 101: 57-66.
- Yao R, Cooper GM (1995) Requirement for phosphatidylinositol-3 kinase in the prevention of apoptosis by nerve growth factor. *Science* 267: 2003-2006.
- Yasuda S, Inoue K, Hirabayashi M, Higashiyama H, Yamamoto Y, Fuyuhiro H, Komure O, Tanaka F, Sobue G, Tsuchiya K, Hamada K, Sasaki H, Takeda K, Ichijo H, Kakizuka A (1999) Triggering of neuronal cell death by accumulation of activated SEK1 on nuclear polyglutamine aggregations in PML bodies. *Genes Cells* 4: 743-756.
- Yohrling GJ, Jiang GC, DeJohn MM, Miller DW, Young AB, Vrana KE, Cha JH (2003) Analysis of cellular, transgenic and human models of Huntington's disease reveals tyrosine hydroxylase alterations and substantia nigra neuropathology. *Brain Res Mol Brain Res* 119: 28-36.
- York RD, Yao H, Dillon T, Ellig CL, Eckert SP, McCleskey EW, Stork PJ (1998) Rap1 mediates sustained MAP kinase activation induced by nerve growth factor. *Nature* 392: 622-626.
- Young AB, Greenamyre JT, Hollingsworth Z, Albin R, D'Amato C, Shoulson I, Penney JB (1988) NMDA receptor losses in putamen from patients with Huntington's disease. *Science* 241: 981-983.
- Zaccaro MC, Ivanisevic L, Perez P, Meakin SO, Saragovi HU (2001) p75 Co-receptors regulate ligand-dependent and ligand-independent Trk receptor activation, in part by altering Trk docking subdomains. *J Biol Chem* 276: 31023-31029.
- Zebisch A, Czernilofsky AP, Keri G, Smigelskaite J, Sill H, Troppmair J (2007) Signaling through RAS-RAF-MEK-ERK: from basics to bedside. *Curr Med Chem* 14: 601-623.
- Zeitlin S, Liu JP, Chapman DL, Papaioannou VE, Efstratiadis A (1995) Increased apoptosis and early embryonic lethality in mice nullizygous for the Huntington's disease gene homologue. *Nat Genet* 11: 155-163.

- Zeron MM, Hansson O, Chen N, Wellington CL, Leavitt BR, Brundin P, Hayden MR, Raymond LA (2002) Increased sensitivity to N-methyl-D-aspartate receptor-mediated excitotoxicity in a mouse model of Huntington's disease. *Neuron* 33: 849-860.
- Zeron MM, Fernandes HB, Krebs C, Shehadeh J, Wellington CL, Leavitt BR, Bainbridge KG, Hayden MR, Raymond LA (2004) Potentiation of NMDA receptor-mediated excitotoxicity linked with intrinsic apoptotic pathway in YAC transgenic mouse model of Huntington's disease. *Mol Cell Neurosci* 25: 469-479.
- Zhang H, Li Q, Graham RK, Slow E, Hayden MR, Bezprozvanny I (2008) Full length mutant huntingtin is required for altered Ca²⁺ signaling and apoptosis of striatal neurons in the YAC mouse model of Huntington's disease. *Neurobiol Dis* 31: 80-88.
- Zhang Y, Li M, Drozda M, Chen M, Ren S, Mejia Sanchez RO, Leavitt BR, Cattaneo E, Ferrante RJ, Hayden MR, Friedlander RM (2003) Depletion of wild-type huntingtin in mouse models of neurologic diseases. *J Neurochem* 87: 101-106.
- Zhang Y, Leavitt BR, van Raamsdonk JM, Dragatsis I, Goldowitz D, MacDonald ME, Hayden MR, Friedlander RM (2006) Huntingtin inhibits caspase-3 activation. *EMBO J* 25: 5896-5906.
- Zheng M, Leung CL, Liem RK (1998) Region-specific expression of cyclin-dependent kinase 5 (cdk5) and its activators, p35 and p39, in the developing and adult rat central nervous system. *J Neurobiol* 35: 141-159.
- Zheng TS, Hunot S, Kuida K, Flavell RA (1999) Caspase knockouts: matters of life and death. *Cell Death Differ* 6: 1043-1053.
- Zhu JH, Kulich SM, Oury TD, Chu CT (2002) Cytoplasmic aggregates of phosphorylated extracellular signal-regulated protein kinases in Lewy body diseases. *Am J Pathol* 161: 2087-2098.
- Zuccato C, Ciarmmola A, Rigamonti D, Leavitt BR, Goffredo D, Conti L, MacDonald ME, Friedlander RM, Silani V, Hayden MR, Timmus T, Sipione S, Cattaneo E (2001) Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. *Science* 293: 493-498.
- Zuccato C, Tartari M, Crotti A, Goffredo D, Valenza M, Conti L, Cataudella T, Leavitt BR, Hayden MR, Timmus T, Rigamonti D, Cattaneo E (2003) Huntingtin interacts with REST/NRSF to modulate the transcription of NRSE-controlled neuronal genes. *Nat Genet* 35: 76-83.
- Zuccato C, Marullo M, Conforti P, MacDonald ME, Tartari M, Cattaneo E (2008) Systematic assessment of BDNF and its receptor levels in human cortices affected by Huntington's disease. *Brain Pathol* 18: 225-238.
- Zukerberg LR, Patrick GN, Nikolic M, Humbert S, Wu CL, Lanier LM, Gertler FB, Vidal M, Van Etten RA, Tsai LH (2000) Cables links Cdk5 and c-Abl and facilitates Cdk5 tyrosine phosphorylation, kinase upregulation, and neurite outgrowth. *Neuron* 26: 633-646.