Identification and Analysis of the Two *Tau* Paralogues in Zebrafish

Mengqi Chen

Supervised by Michael Lardelli and Frank Grützner

Discipline of Genetics

School of Molecular and Biomedical Science

The University of Adelaide

AUSTRALIA

July 2009

References

[1] Ballatore C, Lee VM, Trojanowski JQ (2007) Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. *Nat Rev Neurosci* **8**, 663-672.

[2] Hutton M, Lendon CL, Rizzu P, Baker M, Froelich S, Houlden H, Pickering-Brown S, Chakraverty S, Isaacs A, Grover A, Hackett J, Adamson J, Lincoln S, Dickson D, Davies P, Petersen RC, Stevens M, de Graaff E, Wauters E, van Baren J, Hillebrand M, Joosse M, Kwon JM, Nowotny P, Che LK, Norton J, Morris JC, Reed LA, Trojanowski J, Basun H, Lannfelt L, Neystat M, Fahn S, Dark F, Tannenberg T, Dodd PR, Hayward N, Kwok JB, Schofield PR, Andreadis A, Snowden J, Craufurd D, Neary D, Owen F, Oostra BA, Hardy J, Goate A, van Swieten J, Mann D, Lynch T, Heutink P (1998) Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature* **393**, 702-705.

[3] Poorkaj P, Bird TD, Wijsman E, Nemens E, Garruto RM, Anderson L, Andreadis A, Wiederholt WC, Raskind M, Schellenberg GD (1998) Tau is a candidate gene for chromosome 17 frontotemporal dementia. *Ann Neurol* **43**, 815-825.

[4] Spillantini MG, Murrell JR, Goedert M, Farlow MR, Klug A, Ghetti B (1998) Mutation in the tau gene in familial multiple system tauopathy with presenile dementia. *Proc Natl Acad Sci U S A* **95**, 7737-7741.

[5] Neve RL, Harris P, Kosik KS, Kurnit DM, Donlon TA (1986) Identification of cDNA clones for the human microtubule-associated protein tau and chromosomal localization of the genes for tau and microtubule-associated protein 2. *Brain Res* **387**, 271-280.

[6] Andreadis A, Brown WM, Kosik KS (1992) Structure and novel exons of the human tau gene. *Biochemistry* **31**, 10626-10633.

[7] Wang Y, Loomis PA, Zinkowski RP, Binder LI (1993) A novel tau transcript in cultured human neuroblastoma cells expressing nuclear tau. *J Cell Biol* **121**, 257-267.

[8] Goedert M, Spillantini MG, Jakes R, Rutherford D, Crowther RA (1989) Multiple isoforms of human microtubule-associated protein tau: sequences and localization in neurofibrillary tangles of Alzheimer's disease. *Neuron* **3**, 519-526.

[9] Nunez J, Fischer I (1997) Microtubule-associated proteins (MAPs) in the peripheral nervous system during development and regeneration. *J Mol Neurosci* **8**, 207-222.

[10] Sadot E, Marx R, Barg J, Behar L, Ginzburg I (1994) Complete sequence of 3'-untranslated region of Tau from rat central nervous system. Implications for mRNA heterogeneity. *J Mol Biol* **241**, 325-331.

[11] Veo BL, Krushel LA (2009) Translation initiation of the human tau mRNA through an internal ribosomal entry site. *J Alzheimers Dis* **16**, 271-275.

[12] Andreadis A (2005) Tau gene alternative splicing: expression patterns, regulation and modulation of function in normal brain and neurodegenerative diseases. *Biochim Biophys Acta* **1739**, 91-103.

[13] Brandt R, Leger J, Lee G (1995) Interaction of tau with the neural plasma

membrane mediated by tau's amino-terminal projection domain. *J Cell Biol* **131**, 1327-1340.

[14] Chen J, Kanai Y, Cowan NJ, Hirokawa N (1992) Projection domains of MAP2 and tau determine spacings between microtubules in dendrites and axons. *Nature* **360**, 674-677.

[15] Frappier TF, Georgieff IS, Brown K, Shelanski ML (1994) tau Regulation of microtubule-microtubule spacing and bundling. *J Neurochem* **63**, 2288-2294.

[16] Goedert M, Spillantini MG, Crowther RA (1992) Cloning of a big tau microtubule-associated protein characteristic of the peripheral nervous system. *Proc Natl Acad Sci U S A* **89**, 1983-1987.

[17] Lee G, Neve RL, Kosik KS (1989) The microtubule binding domain of tau protein. *Neuron* **2**, 1615-1624.

[18] Goode BL, Denis PE, Panda D, Radeke MJ, Miller HP, Wilson L, Feinstein SC (1997) Functional interactions between the proline-rich and repeat regions of tau enhance microtubule binding and assembly. *Mol Biol Cell* **8**, 353-365.

[19] Rademakers R, Cruts M, van Broeckhoven C (2004) The role of tau (MAPT) in frontotemporal dementia and related tauopathies. *Hum Mutat* **24**, 277-295.

[20] Himmler A, Drechsel D, Kirschner MW, Martin DW, Jr. (1989) Tau consists of a set of proteins with repeated C-terminal microtubule-binding domains and variable N-terminal domains. *Mol Cell Biol* **9**, 1381-1388.

[21] Kosik KS, Orecchio LD, Bakalis S, Neve RL (1989) Developmentally regulated expression of specific tau sequences. *Neuron* **2**, 1389-1397.

[22] Takuma H, Arawaka S, Mori H (2003) Isoforms changes of tau protein during development in various species. *Brain Res Dev Brain Res* **142**, 121-127.

[23] Hong M, Zhukareva V, Vogelsberg-Ragaglia V, Wszolek Z, Reed L, Miller BI, Geschwind DH, Bird TD, McKeel D, Goate A, Morris JC, Wilhelmsen KC, Schellenberg GD, Trojanowski JQ, Lee VM (1998) Mutation-specific functional impairments in distinct tau isoforms of hereditary FTDP-17. *Science* **282**, 1914-1917.

[24] Zhukareva V, Joyce S, Schuck T, Van Deerlin V, Hurtig H, Albin R, Gilman S, Chin S, Miller B, Trojanowski JQ, Lee VM (2006) Unexpected abundance of pathological tau in progressive supranuclear palsy white matter. *Ann Neurol* **60**, 335-345.

[25] Arai T, Ikeda K, Akiyama H, Shikamoto Y, Tsuchiya K, Yagishita S, Beach T, Rogers J, Schwab C, McGeer PL (2001) Distinct isoforms of tau aggregated in neurons and glial cells in brains of patients with Pick's disease, corticobasal degeneration and progressive supranuclear palsy. *Acta Neuropathol* **101**, 167-173.

[26] Bunker JM, Kamath K, Wilson L, Jordan MA, Feinstein SC (2006) FTDP-17 mutations compromise the ability of tau to regulate microtubule dynamics in cells. *J Biol Chem* **281**, 11856-11863.

[27] Arrasate M, Perez M, Armas-Portela R, Avila J (1999) Polymerization of tau peptides into fibrillar structures. The effect of FTDP-17 mutations. *FEBS Lett* **446**, 199-202.

[28] Goedert M, Jakes R (2005) Mutations causing neurodegenerative tauopathies.

Biochim Biophys Acta **1739**, 240-250.

[29] Stanford PM, Halliday GM, Brooks WS, Kwok JB, Storey CE, Creasey H, Morris JG, Fulham MJ, Schofield PR (2000) Progressive supranuclear palsy pathology caused by a novel silent mutation in exon 10 of the tau gene: expansion of the disease phenotype caused by tau gene mutations. *Brain* **123 (Pt 5)**, 880-893.

[30] Lindquist SG, Holm IE, Schwartz M, Law I, Stokholm J, Batbayli M, Waldemar G, Nielsen JE (2008) Alzheimer disease-like clinical phenotype in a family with FTDP-17 caused by a MAPT R406W mutation. *Eur J Neurol* **15**, 377-385.

[31] Baker M, Litvan I, Houlden H, Adamson J, Dickson D, Perez-Tur J, Hardy J, Lynch T, Bigio E, Hutton M (1999) Association of an extended haplotype in the tau gene with progressive supranuclear palsy. *Hum Mol Genet* **8**, 711-715.

[32] Houlden H, Baker M, Morris HR, MacDonald N, Pickering-Brown S, Adamson J, Lees AJ, Rossor MN, Quinn NP, Kertesz A, Khan MN, Hardy J, Lantos PL, St George-Hyslop P, Munoz DG, Mann D, Lang AE, Bergeron C, Bigio EH, Litvan I, Bhatia KP, Dickson D, Wood NW, Hutton M (2001) Corticobasal degeneration and progressive supranuclear palsy share a common tau haplotype. *Neurology* **56**, 1702-1706.

[33] Di Maria E, Tabaton M, Vigo T, Abbruzzese G, Bellone E, Donati C, Frasson E, Marchese R, Montagna P, Munoz DG, Pramstaller PP, Zanusso G, Ajmar F, Mandich P (2000) Corticobasal degeneration shares a common genetic background with progressive supranuclear palsy. *Ann Neurol* **47**, 374-377.

[34] Myers AJ, Kaleem M, Marlowe L, Pittman AM, Lees AJ, Fung HC, Duckworth J, Leung D, Gibson A, Morris CM, de Silva R, Hardy J (2005) The H1c haplotype at the MAPT locus is associated with Alzheimer's disease. *Hum Mol Genet* **14**, 2399-2404.

[35] Myers AJ, Pittman AM, Zhao AS, Rohrer K, Kaleem M, Marlowe L, Lees A, Leung D, McKeith IG, Perry RH, Morris CM, Trojanowski JQ, Clark C, Karlawish J, Arnold S, Forman MS, Van Deerlin V, de Silva R, Hardy J (2007) The MAPT H1c risk haplotype is associated with increased expression of tau and especially of 4 repeat containing transcripts. *Neurobiol Dis* **25**, 561-570.

[36] Kwok JB, Teber ET, Loy C, Hallupp M, Nicholson G, Mellick GD, Buchanan DD, Silburn PA, Schofield PR (2004) Tau haplotypes regulate transcription and are associated with Parkinson's disease. *Ann Neurol* **55**, 329-334.

[37] Caffrey TM, Joachim C, Paracchini S, Esiri MM, Wade-Martins R (2006) Haplotype-specific expression of exon 10 at the human MAPT locus. *Hum Mol Genet* **15**, 3529-3537.

[38] Caffrey TM, Joachim C, Wade-Martins R (2008) Haplotype-specific expression of the N-terminal exons 2 and 3 at the human MAPT locus. *Neurobiol Aging* **29**, 1923-1929.

[39] Himmler A (1989) Structure of the bovine tau gene: alternatively spliced transcripts generate a protein family. *Mol Cell Biol* **9**, 1389-1396.

[40] Li K, Arikan MC, Andreadis A (2003) Modulation of the membrane-binding domain of tau protein: splicing regulation of exon 2. *Brain Res Mol Brain Res* **116**, 94-105.

[41] Andreadis A, Broderick JA, Kosik KS (1995) Relative exon affinities and suboptimal splice site signals lead to non-equivalence of two cassette exons. *Nucleic Acids Res* **23**, 3585-3593.

[42] Arikan MC, Memmott J, Broderick JA, Lafyatis R, Screaton G, Stamm S, Andreadis A (2002) Modulation of the membrane-binding projection domain of tau protein: splicing regulation of exon 3. *Brain Res Mol Brain Res* **101**, 109-121.

[43] Gao QS, Memmott J, Lafyatis R, Stamm S, Screaton G, Andreadis A (2000) Complex regulation of tau exon 10, whose missplicing causes frontotemporal dementia. *J Neurochem* **74**, 490-500.

[44] Grover A, Houlden H, Baker M, Adamson J, Lewis J, Prihar G, Pickering-Brown S, Duff K, Hutton M (1999) 5' splice site mutations in tau associated with the inherited dementia FTDP-17 affect a stem-loop structure that regulates alternative splicing of exon 10. *J Biol Chem* **274**, 15134-15143.

[45] Donahue CP, Muratore C, Wu JY, Kosik KS, Wolfe MS (2006) Stabilization of the tau exon 10 stem loop alters pre-mRNA splicing. *J Biol Chem* **281**, 23302-23306.

[46] D'Souza I, Schellenberg GD (2002) tau Exon 10 expression involves a bipartite intron 10 regulatory sequence and weak 5' and 3' splice sites. *J Biol Chem* **277**, 26587-26599.

[47] D'Souza I, Poorkaj P, Hong M, Nochlin D, Lee VM, Bird TD, Schellenberg GD (1999) Missense and silent tau gene mutations cause frontotemporal dementia with parkinsonism-chromosome 17 type, by affecting multiple alternative RNA splicing regulatory elements. *Proc Natl Acad Sci U S A* **96**, 5598-5603.

[48] D'Souza I, Schellenberg GD (2000) Determinants of 4-repeat tau expression. Coordination between enhancing and inhibitory splicing sequences for exon 10 inclusion. *J Biol Chem* **275**, 17700-17709.

[49] Grover A, DeTure M, Yen SH, Hutton M (2002) Effects on splicing and protein function of three mutations in codon N296 of tau in vitro. *Neurosci Lett* **323**, 33-36.

[50] Jiang Z, Tang H, Havlioglu N, Zhang X, Stamm S, Yan R, Wu JY (2003) Mutations in tau gene exon 10 associated with FTDP-17 alter the activity of an exonic splicing enhancer to interact with Tra2 beta. *J Biol Chem* **278**, 18997-19007.

[51] Hartmann AM, Rujescu D, Giannakouros T, Nikolakaki E, Goedert M, Mandelkow EM, Gao QS, Andreadis A, Stamm S (2001) Regulation of alternative splicing of human tau exon 10 by phosphorylation of splicing factors. *Mol Cell Neurosci* **18**, 80-90.

[52] Hernandez F, Perez M, Lucas JJ, Mata AM, Bhat R, Avila J (2004) Glycogen synthase kinase-3 plays a crucial role in tau exon 10 splicing and intranuclear distribution of SC35. Implications for Alzheimer's disease. *J Biol Chem* **279**, 3801-3806.

[53] Wang JZ, Liu F (2008) Microtubule-associated protein tau in development, degeneration and protection of neurons. *Prog Neurobiol* **85**, 148-175.

[54] Takashima A (2008) Hyperphosphorylated tau is a cause of neuronal dysfunction in tauopathy. *J Alzheimers Dis* **14**, 371-375.

[55] Khatoon S, Grundke-Iqbal I, Iqbal K (1992) Brain levels of microtubule-associated protein tau are elevated in Alzheimer's disease: a radioimmuno-slot-blot assay for

nanograms of the protein. *J Neurochem* **59**, 750-753.

[56] Khatoon S, Grundke-Iqbal I, Iqbal K (1994) Levels of normal and abnormally phosphorylated tau in different cellular and regional compartments of Alzheimer disease and control brains. *FEBS Lett* **351**, 80-84.

[57] Mazanetz MP, Fischer PM (2007) Untangling tau hyperphosphorylation in drug design for neurodegenerative diseases. *Nat Rev Drug Discov* **6**, 464-479.

[58] Stoothoff WH, Johnson GV (2005) Tau phosphorylation: physiological and pathological consequences. *Biochim Biophys Acta* **1739**, 280-297.

[59] Arendt T, Stieler J, Strijkstra AM, Hut RA, Rudiger J, Van der Zee EA, Harkany T, Holzer M, Hartig W (2003) Reversible paired helical filament-like phosphorylation of tau is an adaptive process associated with neuronal plasticity in hibernating animals. *J Neurosci* **23**, 6972-6981.

[60] Su B, Wang X, Drew KL, Perry G, Smith MA, Zhu X (2008) Physiological regulation of tau phosphorylation during hibernation. *J Neurochem*.

[61] Andorfer C, Acker CM, Kress Y, Hof PR, Duff K, Davies P (2005) Cell-cycle reentry and cell death in transgenic mice expressing nonmutant human tau isoforms. *J Neurosci* **25**, 5446-5454.

[62] Khurana V, Feany MB (2007) Connecting cell-cycle activation to neurodegeneration in Drosophila. *Biochim Biophys Acta* **1772**, 446-456.

[63] Biernat J, Wu YZ, Timm T, Zheng-Fischhofer Q, Mandelkow E, Meijer L, Mandelkow EM (2002) Protein kinase MARK/PAR-1 is required for neurite outgrowth and establishment of neuronal polarity. *Mol Biol Cell* **13**, 4013-4028.

[64] Abraha A, Ghoshal N, Gamblin TC, Cryns V, Berry RW, Kuret J, Binder LI (2000) C-terminal inhibition of tau assembly in vitro and in Alzheimer's disease. *J Cell Sci* **113 Pt 21**, 3737-3745.

[65] Horowitz PM, Patterson KR, Guillozet-Bongaarts AL, Reynolds MR, Carroll CA, Weintraub ST, Bennett DA, Cryns VL, Berry RW, Binder LI (2004) Early N-terminal changes and caspase-6 cleavage of tau in Alzheimer's disease. *J Neurosci* **24**, 7895-7902.

[66] Garcia-Sierra F, Ghoshal N, Quinn B, Berry RW, Binder LI (2003) Conformational changes and truncation of tau protein during tangle evolution in Alzheimer's disease. *J Alzheimers Dis* **5**, 65-77.

[67] Binder LI, Guillozet-Bongaarts AL, Garcia-Sierra F, Berry RW (2005) Tau, tangles, and Alzheimer's disease. *Biochim Biophys Acta* **1739**, 216-223.

[68] Wischik CM (1989) Cell biology of the Alzheimer tangle. *Curr Opin Cell Biol* **1**, 115-122.

[69] Gamblin TC, Chen F, Zambrano A, Abraha A, Lagalwar S, Guillozet AL, Lu M, Fu Y, Garcia-Sierra F, LaPointe N, Miller R, Berry RW, Binder LI, Cryns VL (2003) Caspase cleavage of tau: linking amyloid and neurofibrillary tangles in Alzheimer's disease. *Proc Natl Acad Sci U S A* **100**, 10032-10037.

[70] Yin H, Kuret J (2006) C-terminal truncation modulates both nucleation and extension phases of tau fibrillization. *FEBS Lett* **580**, 211-215.

[71] Braak E, Braak H, Mandelkow EM (1994) A sequence of cytoskeleton changes related to the formation of neurofibrillary tangles and neuropil threads. *Acta*

Neuropathol **87**, 554-567.

[72] Guillozet-Bongaarts AL, Garcia-Sierra F, Reynolds MR, Horowitz PM, Fu Y, Wang T, Cahill ME, Bigio EH, Berry RW, Binder LI (2005) Tau truncation during neurofibrillary tangle evolution in Alzheimer's disease. *Neurobiol Aging* **26**, 1015-1022.

[73] Perry G, Friedman R, Shaw G, Chau V (1987) Ubiquitin is detected in neurofibrillary tangles and senile plaque neurites of Alzheimer disease brains. *Proc Natl Acad Sci U S A* **84**, 3033-3036.

[74] Cripps D, Thomas SN, Jeng Y, Yang F, Davies P, Yang AJ (2006) Alzheimer disease-specific conformation of hyperphosphorylated paired helical filament-Tau is polyubiquitinated through Lys-48, Lys-11, and Lys-6 ubiquitin conjugation. *J Biol Chem* **281**, 10825-10838.

[75] Avila J, Lucas JJ, Perez M, Hernandez F (2004) Role of tau protein in both physiological and pathological conditions. *Physiol Rev* **84**, 361-384.

[76] Petrucelli L, Dickson D, Kehoe K, Taylor J, Snyder H, Grover A, De Lucia M, McGowan E, Lewis J, Prihar G, Kim J, Dillmann WH, Browne SE, Hall A, Voellmy R, Tsuboi Y, Dawson TM, Wolozin B, Hardy J, Hutton M (2004) CHIP and Hsp70 regulate tau ubiquitination, degradation and aggregation. *Hum Mol Genet* **13**, 703-714.

[77] Shimura H, Schwartz D, Gygi SP, Kosik KS (2004) CHIP-Hsc70 complex ubiquitinates phosphorylated tau and enhances cell survival. *J Biol Chem* **279**, 4869-4876.

[78] Zhang YJ, Xu YF, Liu XH, Li D, Yin J, Liu YH, Chen XQ, Wang JZ (2008) Carboxyl terminus of heat-shock cognate 70-interacting protein degrades tau regardless its phosphorylation status without affecting the spatial memory of the rats. *J Neural Transm* **115**, 483-491.

[79] Sahara N, Murayama M, Mizoroki T, Urushitani M, Imai Y, Takahashi R, Murata S, Tanaka K, Takashima A (2005) In vivo evidence of CHIP up-regulation attenuating tau aggregation. *J Neurochem* **94**, 1254-1263.

[80] Keller JN, Hanni KB, Markesbery WR (2000) Impaired proteasome function in Alzheimer's disease. *J Neurochem* **75**, 436-439.

[81] Wang JZ, Grundke-Iqbal I, Iqbal K (1996) Glycosylation of microtubule-associated protein tau: an abnormal posttranslational modification in Alzheimer's disease. *Nat Med* **2**, 871-875.

[82] Castegna A, Thongboonkerd V, Klein JB, Lynn B, Markesbery WR, Butterfield DA (2003) Proteomic identification of nitrated proteins in Alzheimer's disease brain. *J Neurochem* **85**, 1394-1401.

[83] Ledesma MD, Bonay P, Colaco C, Avila J (1994) Analysis of microtubule-associated protein tau glycation in paired helical filaments. *J Biol Chem* **269**, 21614-21619.

[84] Liu F, Iqbal K, Grundke-Iqbal I, Hart GW, Gong CX (2004) O-GlcNAcylation regulates phosphorylation of tau: a mechanism involved in Alzheimer's disease. *Proc Natl Acad Sci U S A* **101**, 10804-10809.

[85] Gong CX, Liu F, Grundke-Iqbal I, Iqbal K (2006) Impaired brain glucose

metabolism leads to Alzheimer neurofibrillary degeneration through a decrease in tau O-GlcNAcylation. *J Alzheimers Dis* **9**, 1-12.

[86] Mandell JW, Banker GA (1996) A spatial gradient of tau protein phosphorylation in nascent axons. *J Neurosci* **16**, 5727-5740.

[87] Dotti CG, Banker GA, Binder LI (1987) The expression and distribution of the microtubule-associated proteins tau and microtubule-associated protein 2 in hippocampal neurons in the rat in situ and in cell culture. *Neuroscience* **23**, 121-130.

[88] Reusche E (1991) Silver staining of senile plaques and neurofibrillary tangles in paraffin sections. A simple and effective method. *Pathol Res Pract* **187**, 1045-1049.

[89] Fujino Y, Wang DS, Thomas N, Espinoza M, Davies P, Dickson DW (2005) Increased frequency of argyrophilic grain disease in Alzheimer disease with 4R tau-specific immunohistochemistry. *J Neuropathol Exp Neurol* **64**, 209-214.

[90] Zhukareva V, Mann D, Pickering-Brown S, Uryu K, Shuck T, Shah K, Grossman M, Miller BL, Hulette CM, Feinstein SC, Trojanowski JQ, Lee VM (2002) Sporadic Pick's disease: a tauopathy characterized by a spectrum of pathological tau isoforms in gray and white matter. *Ann Neurol* **51**, 730-739.

[91] Heutink P (2000) Untangling tau-related dementia. *Hum Mol Genet* **9**, 979-986.

[92] Stanford PM, Shepherd CE, Halliday GM, Brooks WS, Schofield PW, Brodaty H, Martins RN, Kwok JB, Schofield PR (2003) Mutations in the tau gene that cause an increase in three repeat tau and frontotemporal dementia. *Brain* **126**, 814-826.

[93] van Swieten JC, Stevens M, Rosso SM, Rizzu P, Joosse M, de Koning I, Kamphorst W, Ravid R, Spillantini MG, Niermeijer, Heutink P (1999) Phenotypic variation in hereditary frontotemporal dementia with tau mutations. *Ann Neurol* **46**, 617-626.

[94] Reed LA, Schmidt ML, Wszolek ZK, Balin BJ, Soontornniyomkij V, Lee VM, Trojanowski JQ, Schelper RL (1998) The neuropathology of a chromosome 17-linked autosomal dominant parkinsonism and dementia ("pallido-ponto-nigral degeneration"). *J Neuropathol Exp Neurol* **57**, 588-601.

[95] Sergeant N, David JP, Goedert M, Jakes R, Vermersch P, Buee L, Lefranc D, Wattez A, Delacourte A (1997) Two-dimensional characterization of paired helical filament-tau from Alzheimer's disease: demonstration of an additional 74-kDa component and age-related biochemical modifications. *J Neurochem* **69**, 834-844.

[96] Togo T, Akiyama H, Iseki E, Uchikado H, Kondo H, Ikeda K, Tsuchiya K, de Silva R, Lees A, Kosaka K (2004) Immunohistochemical study of tau accumulation in early stages of Alzheimer-type neurofibrillary lesions. *Acta Neuropathol* **107**, 504-508.

[97] Hanes J, Zilka N, Bartkova M, Caletkova M, Dobrota D, Novak M (2009) Rat tau proteome consists of six tau isoforms: implication for animal models of human tauopathies. *J Neurochem* **108**, 1167-1176.

[98] Terwel D, Lasrado R, Snauwaert J, Vandeweert E, Van Haesendonck C, Borghgraef P, Van Leuven F (2005) Changed conformation of mutant Tau-P301L underlies the moribund tauopathy, absent in progressive, nonlethal axonopathy of Tau-4R/2N transgenic mice. *J Biol Chem* **280**, 3963-3973.

[99] Andorfer C, Kress Y, Espinoza M, de Silva R, Tucker KL, Barde YA, Duff K,

Davies P (2003) Hyperphosphorylation and aggregation of tau in mice expressing normal human tau isoforms. *J Neurochem* **86**, 582-590.

[100] Gong CX, Liu F, Grundke-Iqbal I, Iqbal K (2005) Post-translational modifications of tau protein in Alzheimer's disease. *J Neural Transm* **112**, 813-838.

[101] Sengupta A, Kabat J, Novak M, Wu Q, Grundke-Iqbal I, Iqbal K (1998) Phosphorylation of tau at both Thr 231 and Ser 262 is required for maximal inhibition of its binding to microtubules. *Arch Biochem Biophys* **357**, 299-309.

[102] Alonso Adel C, Mederlyova A, Novak M, Grundke-Iqbal I, Iqbal K (2004) Promotion of hyperphosphorylation by frontotemporal dementia tau mutations. *J Biol Chem* **279**, 34873-34881.

[103] Gong CX, Iqbal K (2008) Hyperphosphorylation of microtubule-associated protein tau: a promising therapeutic target for Alzheimer disease. *Curr Med Chem* **15**, 2321-2328.

[104] Ferrer I, Gomez-Isla T, Puig B, Freixes M, Ribe E, Dalfo E, Avila J (2005) Current advances on different kinases involved in tau phosphorylation, and implications in Alzheimer's disease and tauopathies. *Curr Alzheimer Res* **2**, 3-18.

[105] Li X, Lu F, Tian Q, Yang Y, Wang Q, Wang JZ (2006) Activation of glycogen synthase kinase-3 induces Alzheimer-like tau hyperphosphorylation in rat hippocampus slices in culture. *J Neural Transm* **113**, 93-102.

[106] Lovestone S, Reynolds CH, Latimer D, Davis DR, Anderton BH, Gallo JM, Hanger D, Mulot S, Marquardt B, Stabel S, et al. (1994) Alzheimer's disease-like phosphorylation of the microtubule-associated protein tau by glycogen synthase kinase-3 in transfected mammalian cells. *Curr Biol* **4**, 1077-1086.

[107] Lucas JJ, Hernandez F, Gomez-Ramos P, Moran MA, Hen R, Avila J (2001) Decreased nuclear beta-catenin, tau hyperphosphorylation and neurodegeneration in GSK-3beta conditional transgenic mice. *Embo J* **20**, 27-39.

[108] Mateo I, Infante J, Llorca J, Rodriguez E, Berciano J, Combarros O (2006) Association between glycogen synthase kinase-3beta genetic polymorphism and late-onset Alzheimer's disease. *Dement Geriatr Cogn Disord* **21**, 228-232.

[109] Jope RS, Johnson GV (2004) The glamour and gloom of glycogen synthase kinase-3. *Trends Biochem Sci* **29**, 95-102.

[110] Kang DE, Yoon IS, Repetto E, Busse T, Yermian N, Ie L, Koo EH (2005) Presenilins mediate phosphatidylinositol 3-kinase/AKT and ERK activation via select signaling receptors. Selectivity of PS2 in platelet-derived growth factor signaling. *J Biol Chem* **280**, 31537-31547.

[111] Liu SJ, Zhang AH, Li HL, Wang Q, Deng HM, Netzer WJ, Xu H, Wang JZ (2003) Overactivation of glycogen synthase kinase-3 by inhibition of phosphoinositol-3 kinase and protein kinase C leads to hyperphosphorylation of tau and impairment of spatial memory. *J Neurochem* **87**, 1333-1344.

[112] Ramos AM, Fernandez C, Amran D, Esteban D, de Blas E, Palacios MA, Aller P (2006) Pharmacologic inhibitors of extracellular signal-regulated kinase (ERKs) and c-Jun NH(2)-terminal kinase (JNK) decrease glutathione content and sensitize human promonocytic leukemia cells to arsenic trioxide-induced apoptosis. *J Cell Physiol* **209**, 1006-1015.

[113] Liu SJ, Zhang JY, Li HL, Fang ZY, Wang Q, Deng HM, Gong CX, Grundke-Iqbal I, Iqbal K, Wang JZ (2004) Tau becomes a more favorable substrate for GSK-3 when it is prephosphorylated by PKA in rat brain. *J Biol Chem* **279**, 50078-50088.
[114] Tseng HC, Zhou Y, Shen Y, Tsai LH (2002) A survey of Cdk5 activator p35 and p25 levels in Alzheimer's disease brains. *FEBS Lett* **523**, 58-62.
[115] Ahlijanian MK, Barrezueta NX, Williams RD, Jakowski A, Kowsz KP, McCarthy S, Coskran T, Carlo A, Seymour PA, Burkhardt JE, Nelson RB, McNeish JD (2000) Hyperphosphorylated tau and neurofilament and cytoskeletal disruptions in mice overexpressing human p25, an activator of cdk5. *Proc Natl Acad Sci U S A* **97**, 2910-2915.
[116] Takashima A, Murayama M, Yasutake K, Takahashi H, Yokoyama M, Ishiguro K (2001) Involvement of cyclin dependent kinase5 activator p25 on tau phosphorylation in mouse brain. *Neurosci Lett* **306**, 37-40.
[117] Chatterjee S, Sang TK, Lawless GM, Jackson GR (2009) Dissociation of tau toxicity and phosphorylation: role of GSK-3beta, MARK and Cdk5 in a Drosophila model. *Hum Mol Genet* **18**, 164-177.
[118] Plattner F, Angelo M, Giese KP (2006) The roles of cyclin-dependent kinase 5 and glycogen synthase kinase 3 in tau hyperphosphorylation. *J Biol Chem* **281**, 25457-25465.
[119] Liu F, Liang Z, Gong CX (2006) Hyperphosphorylation of tau and protein phosphatases in Alzheimer disease. *Panminerva Med* **48**, 97-108.
[120] Gong CX, Singh TJ, Grundke-Iqbal I, Iqbal K (1993) Phosphoprotein phosphatase activities in Alzheimer disease brain. *J Neurochem* **61**, 921-927.
[121] Vogelsberg-Ragaglia V, Schuck T, Trojanowski JQ, Lee VM (2001) PP2A mRNA expression is quantitatively decreased in Alzheimer's disease hippocampus. *Exp Neurol* **168**, 402-412.
[122] Goedert M, Satumtira S, Jakes R, Smith MJ, Kamibayashi C, White CL, 3rd, Sontag E (2000) Reduced binding of protein phosphatase 2A to tau protein with frontotemporal dementia and parkinsonism linked to chromosome 17 mutations. *J Neurochem* **75**, 2155-2162.
[123] Roy S, Zhang B, Lee VM, Trojanowski JQ (2005) Axonal transport defects: a common theme in neurodegenerative diseases. *Acta Neuropathol* **109**, 5-13.
[124] Ishihara T, Hong M, Zhang B, Nakagawa Y, Lee MK, Trojanowski JQ, Lee VM (1999) Age-dependent emergence and progression of a tauopathy in transgenic mice overexpressing the shortest human tau isoform. *Neuron* **24**, 751-762.
[125] Dawson HN, Ferreira A, Eyster MV, Ghoshal N, Binder LI, Vitek MP (2001) Inhibition of neuronal maturation in primary hippocampal neurons from tau deficient mice. *J Cell Sci* **114**, 1179-1187.
[126] Kosik KS, Caceres A (1991) Tau protein and the establishment of an axonal morphology. *J Cell Sci Suppl* **15**, 69-74.
[127] Trojanowski JQ, Smith AB, Huryn D, Lee VM (2005) Microtubule-stabilising drugs for therapy of Alzheimer's disease and other neurodegenerative disorders with axonal transport impairments. *Expert Opin Pharmacother* **6**, 683-686.
[128] Zhang B, Maiti A, Shively S, Lakhani F, McDonald-Jones G, Bruce J, Lee EB, Xie

SX, Joyce S, Li C, Toleikis PM, Lee VM, Trojanowski JQ (2005) Microtubule-binding drugs offset tau sequestration by stabilizing microtubules and reversing fast axonal transport deficits in a tauopathy model. *Proc Natl Acad Sci U S A* **102**, 227-231.

[129] Harada A, Oguchi K, Okabe S, Kuno J, Terada S, Ohshima T, Sato-Yoshitake R, Takei Y, Noda T, Hirokawa N (1994) Altered microtubule organization in small-calibre axons of mice lacking tau protein. *Nature* **369**, 488-491.

[130] Rapoport M, Dawson HN, Binder LI, Vitek MP, Ferreira A (2002) Tau is essential to beta -amyloid-induced neurotoxicity. *Proc Natl Acad Sci U S A* **99**, 6364-6369.

[131] Khlistunova I, Biernat J, Wang Y, Pickhardt M, von Bergen M, Gazova Z, Mandelkow E, Mandelkow EM (2006) Inducible expression of Tau repeat domain in cell models of tauopathy: aggregation is toxic to cells but can be reversed by inhibitor drugs. *J Biol Chem* **281**, 1205-1214.

[132] Khlistunova I, Pickhardt M, Biernat J, Wang Y, Mandelkow EM, Mandelkow E (2007) Inhibition of tau aggregation in cell models of tauopathy. *Curr Alzheimer Res* **4**, 544-546.

[133] Santacruz K, Lewis J, Spires T, Paulson J, Kotilinek L, Ingelsson M, Guimaraes A, DeTure M, Ramsden M, McGowan E, Forster C, Yue M, Orne J, Janus C, Mariash A, Kuskowski M, Hyman B, Hutton M, Ashe KH (2005) Tau suppression in a neurodegenerative mouse model improves memory function. *Science* **309**, 476-481.

[134] Le Corre S, Klafki HW, Plesnila N, Hubinger G, Obermeier A, Sahagun H, Monse B, Seneci P, Lewis J, Eriksen J, Zehr C, Yue M, McGowan E, Dickson DW, Hutton M, Roder HM (2006) An inhibitor of tau hyperphosphorylation prevents severe motor impairments in tau transgenic mice. *Proc Natl Acad Sci U S A* **103**, 9673-9678.

[135] Cash AD, Aliev G, Siedlak SL, Nunomura A, Fujioka H, Zhu X, Raina AK, Vinters HV, Tabaton M, Johnson AB, Paula-Barbosa M, Avila J, Jones PK, Castellani RJ, Smith MA, Perry G (2003) Microtubule reduction in Alzheimer's disease and aging is independent of tau filament formation. *Am J Pathol* **162**, 1623-1627.

[136] Wittmann CW, Wszolek MF, Shulman JM, Salvaterra PM, Lewis J, Hutton M, Feany MB (2001) Tauopathy in Drosophila: neurodegeneration without neurofibrillary tangles. *Science* **293**, 711-714.

[137] Alonso AC, Grundke-Iqbal I, Iqbal K (1996) Alzheimer's disease hyperphosphorylated tau sequesters normal tau into tangles of filaments and disassembles microtubules. *Nat Med* **2**, 783-787.

[138] Takahashi RH, Capetillo-Zarate E, Lin MT, Milner TA, Gouras GK (2008) Co-occurrence of Alzheimer's disease beta-amyloid and tau pathologies at synapses. *Neurobiol Aging*.

[139] Busciglio J, Lorenzo A, Yeh J, Yankner BA (1995) beta-amyloid fibrils induce tau phosphorylation and loss of microtubule binding. *Neuron* **14**, 879-888.

[140] Wang YP, Wang XC, Tian Q, Yang Y, Zhang Q, Zhang JY, Zhang YC, Wang ZF, Wang Q, Li H, Wang JZ (2006) Endogenous overproduction of beta-amyloid induces tau hyperphosphorylation and decreases the solubility of tau in N2a cells. *J Neural Transm* **113**, 1723-1732.

[141] Gotz J, Chen F, van Dorpe J, Nitsch RM (2001) Formation of neurofibrillary tangles in P301l tau transgenic mice induced by Abeta 42 fibrils. *Science* **293**, 1491-1495.

[142] Lewis J, Dickson DW, Lin WL, Chisholm L, Corral A, Jones G, Yen SH, Sahara N, Skipper L, Yager D, Eckman C, Hardy J, Hutton M, McGowan E (2001) Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP. *Science* **293**, 1487-1491.

[143] Oddo S, Billings L, Kesslak JP, Cribbs DH, LaFerla FM (2004) Abeta immunotherapy leads to clearance of early, but not late, hyperphosphorylated tau aggregates via the proteasome. *Neuron* **43**, 321-332.

[144] Ma QL, Lim GP, Harris-White ME, Yang F, Ambegaokar SS, Ubeda OJ, Glabe CG, Teter B, Frautschy SA, Cole GM (2006) Antibodies against beta-amyloid reduce Abeta oligomers, glycogen synthase kinase-3beta activation and tau phosphorylation in vivo and in vitro. *J Neurosci Res* **83**, 374-384.

[145] Roberson ED, Scearce-Levie K, Palop JJ, Yan F, Cheng IH, Wu T, Gerstein H, Yu GQ, Mucke L (2007) Reducing endogenous tau ameliorates amyloid beta-induced deficits in an Alzheimer's disease mouse model. *Science* **316**, 750-754.

[146] Bowser R, Smith MA (2002) Cell cycle proteins in Alzheimer's disease: plenty of wheels but no cycle. *J Alzheimers Dis* **4**, 249-254.

[147] Hoglinger GU, Breunig JJ, Depboylu C, Rouaux C, Michel PP, Alvarez-Fischer D, Boutillier AL, Degregori J, Oertel WH, Rakic P, Hirsch EC, Hunot S (2007) The pRb/E2F cell-cycle pathway mediates cell death in Parkinson's disease. *Proc Natl Acad Sci U S A* **104**, 3585-3590.

[148] Jordan-Sciutto KL, Malaiyandi LM, Bowser R (2002) Altered distribution of cell cycle transcriptional regulators during Alzheimer disease. *J Neuropathol Exp Neurol* **61**, 358-367.

[149] Zhu X, Siedlak SL, Wang Y, Perry G, Castellani RJ, Cohen ML, Smith MA (2008) Neuronal binucleation in Alzheimer disease hippocampus. *Neuropathol Appl Neurobiol* **34**, 457-465.

[150] Lee HG, Casadesus G, Zhu X, Castellani RJ, McShea A, Perry G, Petersen RB, Bajic V, Smith MA (2009) Cell cycle re-entry mediated neurodegeneration and its treatment role in the pathogenesis of Alzheimer's disease. *Neurochem Int* **54**, 84-88.

[151] Zhu X, Raina AK, Perry G, Smith MA (2004) Alzheimer's disease: the two-hit hypothesis. *Lancet Neurol* **3**, 219-226.

[152] Majd S, Zarifkar A, Rastegar K, Takhshid MA (2008) Different fibrillar Abeta 1-42 concentrations induce adult hippocampal neurons to reenter various phases of the cell cycle. *Brain Res* **1218**, 224-229.

[153] Hoerndli FJ, Pelech S, Papassotiropoulos A, Gotz J (2007) Abeta treatment and P301L tau expression in an Alzheimer's disease tissue culture model act synergistically to promote aberrant cell cycle re-entry. *Eur J Neurosci* **26**, 60-72.

[154] Varvel NH, Bhaskar K, Patil AR, Pimplikar SW, Herrup K, Lamb BT (2008) Abeta oligomers induce neuronal cell cycle events in Alzheimer's disease. *J Neurosci* **28**, 10786-10793.

[155] Pope WB, Lambert MP, Leypold B, Seupaul R, Sletten L, Krafft G, Klein WL (1994)

Microtubule-associated protein tau is hyperphosphorylated during mitosis in the human neuroblastoma cell line SH-SY5Y. *Exp Neurol* **126**, 185-194.

[156] McShea A, Lee HG, Petersen RB, Casadesus G, Vincent I, Linford NJ, Funk JO, Shapiro RA, Smith MA (2007) Neuronal cell cycle re-entry mediates Alzheimer disease-type changes. *Biochim Biophys Acta* **1772**, 467-472.

[157] Park KH, Hallows JL, Chakrabarty P, Davies P, Vincent I (2007) Conditional neuronal simian virus 40 T antigen expression induces Alzheimer-like tau and amyloid pathology in mice. *J Neurosci* **27**, 2969-2978.

[158] Khurana V, Lu Y, Steinhilb ML, Oldham S, Shulman JM, Feany MB (2006) TOR-mediated cell-cycle activation causes neurodegeneration in a Drosophila tauopathy model. *Curr Biol* **16**, 230-241.

[159] Bossing T, Udolph G, Doe CQ, Technau GM (1996) The embryonic central nervous system lineages of Drosophila melanogaster. I. Neuroblast lineages derived from the ventral half of the neuroectoderm. *Dev Biol* **179**, 41-64.

[160] Schmidt H, Rickert C, Bossing T, Vef O, Urban J, Technau GM (1997) The embryonic central nervous system lineages of Drosophila melanogaster. II. Neuroblast lineages derived from the dorsal part of the neuroectoderm. *Dev Biol* **189**, 186-204.

[161] Cambiazo V, Gonzalez M, Maccioni RB (1995) DMAP-85: a tau-like protein from Drosophila melanogaster larvae. *J Neurochem* **64**, 1288-1297.

[162] Takei Y, Teng J, Harada A, Hirokawa N (2000) Defects in axonal elongation and neuronal migration in mice with disrupted tau and map1b genes. *J Cell Biol* **150**, 989-1000.

[163] Denk F, Wade-Martins R (2009) Knock-out and transgenic mouse models of tauopathies. *Neurobiol Aging* **30**, 1-13.

[164] Duff K, Knight H, Refolo LM, Sanders S, Yu X, Picciano M, Malester B, Hutton M, Adamson J, Goedert M, Burki K, Davies P (2000) Characterization of pathology in transgenic mice over-expressing human genomic and cDNA tau transgenes. *Neurobiol Dis* **7**, 87-98.

[165] Oddo S, Caccamo A, Shepherd JD, Murphy MP, Golde TE, Kayed R, Metherate R, Mattson MP, Akbari Y, LaFerla FM (2003) Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. *Neuron* **39**, 409-421.

[166] Tomasiewicz HG, Flaherty DB, Soria JP, Wood JG (2002) Transgenic zebrafish model of neurodegeneration. *J Neurosci Res* **70**, 734-745.

[167] Bai Q, Garver JA, Hukriede NA, Burton EA (2007) Generation of a transgenic zebrafish model of Tauopathy using a novel promoter element derived from the zebrafish eno2 gene. *Nucleic Acids Res* **35**, 6501-6516.

[168] Paquet D, Bhat R, Sydow A, Mandelkow EM, Berg S, Hellberg S, Falting J, Distel M, Koster RW, Schmid B, Haass C (2009) A zebrafish model of tauopathy allows in vivo imaging of neuronal cell death and drug evaluation. *J Clin Invest* **119**, 1382-1395.

[169] Zon LI, Peterson RT (2005) In vivo drug discovery in the zebrafish. *Nat Rev Drug Discov* **4**, 35-44.