STATE OF THE ART

From Tangles to Tau Protein

Iqbal K[1], Novak M[2,3]

[1]*New York State Institute for Basic Research in Developmental Disabilities, Staten Island, New York, USA.* **iqbalk@worldnet.att.net**

Alois Alzheimer couldn't have chosen a name more appropriate than neurofibrillary tangles when one hundred years ago (Alzheimer, 1906) he presented this histopathological hallmark of the progressive dementing disorder, which got named after him as Alzheimer disease. Both, the structure and as well as the molecular composition of neurofibrillary tangles have baffled neuroscientists for many years. It was not till 1963 when with the help of the electron microscope the tangles were found to be made up of paired helical filaments (PHF). It took another 23 years before microtubule associated protein tau was immunohistochemically identified as the part of neurofibrillary tangles (Grundke-Iqbal, 1986 a). The same year it was shown that tau protein in Alzheimer disease brain was abnormally hyperphosphorylated (Grundke-Iqbal, 1986 b). In 1988 Michal Novak, Cesar Milstein and Claude Wischik produced monoclonal antibody that was able to recognize then unknown protein in PHF. The antibody (MN423) allowed its isolation and let to full molecular characterization as protein tau. These studies provided molecular proof that tau protein was the major and an integral component of the PHF (Wischik et al, 1988 a, b, Goedert et al, 1988, Novak et al, 1989, 1991). Over the years the significance of tau pathology for the neurodegenerative diseases was discussed and often questioned. However, detailed studies of the maturation and distribution of NFTs, showing correlation with degree of cognitive decline and memory impairment in Alzheimer's disease (Braak and Braak, 1991), together with discovery of tau gene mutations causing fronto-temporal dementia in many families (Hutton et al, 1998) promoted tau as the major pathogenic force in neurodegenerative cascade.

Further studies focused on tau dysfunctions revealed truncation and phosphorylation as two major posttranslational modifications responsible for toxic gain of function as an underlying cause of tauopathies including Alzheimer's disease (Alonso et al, 1996, Novak et al, 1989, 1991, 1993, Avila et al, 2006). Recently, in vivo experiments using transgenic expression of conformationally modified truncated tau showed that truncation is able to drive neurofibrillary pathology of Alzheimer's type (Zilka et al, 2006). Finally, after one hundred years the exact nature of the neurofibrillary tangles and their role in neurodegeneration is beginning to be unraveled.

References

Alonso AC, Grundke-Iqbal I, Iqbal K. Alzheimer's disease hyperphosphorylated tau sequesters normal tau into tangles of filaments and disassembles microtubules. Nat Med 1996; 2(7): 783—787.

Alzheimer A. Uber einen eigenartigen schweren Erkrankungsprozel – der Hirnrinde. 37th Meeting of Southwest German Psychiatrists, Tübingen 1906.

Avila J. Tau phosphorylation and aggregation in Alzheimer's disease pathology. FEBS Lett 2006; 580 (12): 2922—2927.

Braak H, Braak E. Neuropathological stageing of Alzheimer related changes. Acta Neuropathol 1991; 82: 239—259.

Goedert M, Wischik CM, Crowther RA, Walker JE, Klug A. Cloning and sequencing of the cDNA encoding a core protein of the paired helical filament of Alzheimer disease: identification as the microtubule-associated protein tau. Proc Natl Acad Sci USA 1988; 85 (11): 4051—4055.

Grundke-Iqbal I, Iqbal K, Quinlan M, Tung YC, Zaidi MS, Wisniewski HM. Microtubule-associated protein tau. A component of Alzheimer paired helical filaments. J Biol Chem 1986 a; 261: 6084—6089.

Grundke-Iqbal I, Iqbal K, Tung YC, Quinlan M, Wisniewski HM and Binder LI. Abnormal phosphorylation of the microtubule-associa-

[1]New York State Institute for Basic Research in Developmental Disabilities, Staten Island, New York, USA, [2]Institute of Neuroimmunology, Centre of Excellence, Slovak Academy of Sciences, Bratislava, Slovakia, and [3]Centre of Excellence for Alzheimer's Disease and Related Disorders, Slovakia

Address of correspondence: Khalid Iqbal, PhD, New York State Institute for Basic Research in Developmental Disabilities, Staten Island, New York, USA.

Acknowledgement: This work was supported by research grant VEGA, No. 2/5101/26 and ESF project No. 13120200026.

ted protein tau (tau) in Alzheimer cytoskeletal pathology. Proc Natl Acad Sci USA 1986 b; 83: 4913—4917.

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. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. Nature 1998; 393 (6686): 702—705.

Novak M, Wischik CM, Edwards P, Pannell R, Milstein C. Characterisation of the first monoclonal antibody against the pronase resistant core of the Alzheimer PHF. Prog Clin Biol Res 1989; 317: 755—761.

Novak M, Kabat J, Wischik CM. Molecular characterization of the minimal protease resistant tau unit of the Alzheimer's disease paired helical filament. EMBO J 1993; 12: 365—370.

Novak M, Jakes R, Edwards PC, Milstein C, Wischik CM. Difference between the tau protein of Alzheimer paired helical filament core and normal tau revealed by epitope analysis of monoclonal antibodies 423 and 7.51. Proc Natl Acad Sci USA 1991; 88 (13): 5837—5841.

Wischik CM, Novak M, Thogersen HC, Edwards PC, Runswick MJ, Jakes R, Walker JE, Milstein C, Roth M, Klug A. Isolation of a fragment of tau derived from the core of the paired helical filament of Alzheimer disease. Proc Natl Acad Sci USA 1988; 85: 4506—4510.

Wischik CM, Novak M, Edwards PC, Klug A, Tichelaar W, Crowther RA. Structural characterisation of the core of the paired helical filament of Alzheimer disease. Proc Natl Acad Sci USA 1988; 85: 4884—4888.

Zilka N, Filipcik P, Koson P, Fialova L, Skrabana R, Zilkova M, Rolkova G, Kontsekova E, Novak M. Truncated tau from sporadic Alzheimer's disease suffices to drive neurofibrillary degeneration in vivo. FEBS Lett 2006; 580(15): 3582—3588.

Received June 29, 2006.
Accepted September 2, 2006.