American Journal of Pathology, Vol. 148, No. 2, February 1996
Copyright © American Society for Investigative Pathology

Commentary

The Golgi Apparatus and the Pathogenesis of Alzheimer's Disease

Mauro C. Dal Canto

From the Department of Pathology (Neuropathology), Northwestern University Medical School, Chicago, Illinois

Alois Alzheimer was the first to correlate the development of the most common form of dementia in middle to late life with the presence of pathological changes that are still considered the hallmark of this disease, ie, neurofibrillary tangles (NFTs) and amyloid deposits. Despite an exponential increase in important discoveries, particularly during the last 10 years, the mechanisms leading to the development of these tissue alterations are still largely obscure and often marred in controversy. In this issue, Stieber et al[1] have shifted the focus from NFTs and amyloid deposits to the Golgi apparatus (GA). To understand how this study relates to previous investigations on the pathogenesis of Alzheimer's disease (AD), a brief review of the classical lesions, NFTs and amyloid deposits, is first presented.

NFTs

A milestone in our understanding of the structure and chemical composition of NFTs was the discovery that the main constituent of the characteristic paired helical filaments (PHFs) is hyperphosphorylated tau, one of the microtubule-associated proteins (reviewed in ref. 2). Normal adult tau normally associates with microtubules by its tandem repeat region. Hyperphosphorylation of tau would make this interaction impossible. Lack of binding of tau to microtubules would result in destabilization of these cytoskeletal elements with obvious adverse effects on axoplasmic flow. At the same time, the unassociated hyperphosphorylated tau would self-assemble into PHFs, and, by precipitating to form NFTs, would further damage neurons. There is recent evidence that the hyperphosphorylated state of tau may depend more on deficient phosphatase activity than on abnormally high phosphorylation.[3,4]

Although tau constitutes the main component of NFTs, additional proteins have been shown to participate in the formation of NFTs including α1-antichymotrypsin, ubiquitin, heparan sulfate proteoglycans, fibroblast growth factor (FGF), and apolipoprotein E.[5,6] Recent studies suggest that aluminum may facilitate the precipitation of hyperphosphorylated tau as well as the co-precipitation of the other protein components (reviewed in ref. 5). Aluminum may act by binding to domains on phosphorylated tau containing phosphorylated Ser or other residues, and it can regulate phosphorylation and dephosphorylation of tau. Aluminum is also known to facilitate changes in protein conformation by inducing β-pleated sheet structures. Binding of aluminum, therefore, would further favor aggregation and hamper proteolysis of the abnormal tau.[5] Despite such important advancements in our understanding of tau pathophysiology, it is still unknown whether the various alterations outlined above have any cause-effect relationship with the disease itself.

Amyloid Deposits

The second hallmark lesion in AD is the amyloid plaque. In parallel with researchers in the tau field, several groups working on amyloid have produced important advancements in our understanding of morphological, biochemical, and molecular mechanisms leading to the deposition of this abnormal material in AD brains. The first important discovery was the isolation of amyloid β protein by Glenner and

Accepted for publication November 29, 1995.

Address reprint requests to Mauro C. Dal Canto, M. D., Department of Pathology (Neuropathology), Northwestern University Medical School, 303 East Chicago Avenue, Chicago, IL 60611.

Wong[7] from meningovascular amyloid. Subsequent studies determined that amyloid accumulating in neuropil and in vessels is similar, differing only in the length of fragments from about 40 to 42–43 residues long. It has also been determined that these fragments of varying length derive from the proteolytic breakdown of a larger glycoprotein called amyloid β-protein precursor (βAPP) (for extensive reviews see refs. 8 to 10). This protein is encoded on chromosome 21 and alternate transcripts are recognized. The protein has the general structure of a membrane receptor with a long extracellular N-terminal, a *trans* membrane domain, and a short intracellular C-terminal. Recent studies have shown that cleavage at different sites produce fragments of different lengths.[8–10] The Aβ fragment comprises the first 11–15 residues of the transmembrane domain and extends 28 amino acids into the N-terminal domain. Most recent studies in this field have tried to explain how the precursor protein is processed inside the cell in order to generate and secrete the Aβ fragment. At first, investigators thought that the generation of the Aβ fragment was a highly abnormal process that required some sort of injury to the plasma membrane in order to allow cleavage inside the transmembrane domain. Recently, however, soluble Aβ fragments have been demonstrated in the medium of both untransfected and βAPP-transfected cells, as well as in the cerebro-spinal fluid and serum of control patients, indicating that generation of soluble Aβ fragments may be a normal event.[11–14] If so, then, what determines the neurotoxicity of Aβ? A number of contradictory studies have suggested either a neurotoxic effect, no effect, or a trophic effect on neurons by Aβ. It appears, however, that any effect may depend on the physical conformation of the molecule, since neurotoxic effects may be best observed when Aβ is in an aggregated, β-pleated conformation (reviewed in ref. 9).

The most dramatic advances, in the last few years, have come from the discovery of several genetic forms of the disease which depend on either mutations or different allelic combinations of different genes in different chromosomes. At the time of this writing, chromosomes 21, 19, and 14 have been found to be implicated in different forms of the disease. Chromosome 21 harbors the gene for βAPP, and several missense mutations in this gene have been associated with familial AD with early onset. This has been interpreted as one strong argument in favor of the amyloid hypothesis for AD (reviewed in ref. 8). More recently, the identification of the apoprotein E gene on chromosome 19 as a risk factor in late-onset familial[15] and sporadic AD[16] has been the spark to ignite a series of important studies around the world. Briefly, it has been found that the ε4/ε4 allelic combination predisposes patients to the development of an earlier onset and more severe form of AD[17] while the ε3/ε2, and even more so, the ε2/ε2 allelic combinations would be protective.[18] These studies are important because they dovetail with those on tau and amyloid. It has been shown, in fact, that apo ε4 has more binding affinity for Aβ than ε3, thus possibly favoring its precipitation and the formation of insoluble deposits. It has been suggested that apo ε4 may act as a pathological chaperon, inducing conformational changes particularly on Aβ, that would result in the formation of β-pleated sheet structures, thus facilitating their aggregation and precipitation (reviewed in ref. 19). In addition, apo ε4 appears to have no propensity to bind tau, whereas apo ε3 would have affinity for it, thus preventing its phosphorylation and self-assembly into PHFs.[20] From these studies, apoprotein ε type 4 appears to constitute double jeopardy. On the one hand, it facilitates the aggregation of Aβ, while, on the other, it would lack the ability of protecting tau from phosphorylation, thus favoring self-assembly of hyperphosphorylated tau, formation of NFTs, and lack of microtubule stabilization. There is general agreement, however, that while the expression of apoprotein ε4 constitutes a risk factor for the development of AD, it cannot be considered a causative factor, by itself.

Controversy still reigns in regard to the role of NFTs and amyloid deposits in the pathogenesis of AD. Numerous studies have shown that synaptic loss and the presence of NFTs are the best parameters to correlate with the severity of dementia.[21,22] On the other hand, others argue that amyloid deposition is the only characteristic change of AD since NFTs may also deposit in other diseases without dementia.[8] Alternatively, both NFTs and amyloid deposits may represent the end result of earlier, more subtle pathological processes. Tau, βAPP, and all enzymes involved in their processing and final packaging are normally expressed in neurons. It is possible that alterations at some stage in their synthetic pathway may constitute early events in AD, important for understanding the constellation of pathological changes outlined above.

The paper by Stieber et al[1] in this issue of the Journal is highly relevant to this concept, because it explores the role of the GA in the pathogenesis of AD. The GA has a crucial function in the processing, transport, modification, and targeting of cellular proteins,[23] and it has been shown that the size of the GA has direct relationship with the level of activity of the

cell.[24] Previous work by these investigators, in collaboration with the Amsterdam group of Swaab et al,[25] had shown a significant reduction in the size of the GA in the large neurons of the nucleus basalis of Meynert before any decrease in size of the same neurons could be observed. This indicated that the overall activity of neurons in the nucleus basalis of Meynert was severely depressed.[25] In a later paper, these authors showed that a population of neurons without NFTs showed atrophy of the GA, indicating that decreased activity in these neurons was not necessarily related to the presence of NFTs.[26] In this issue, Stieber et al[1] report that, in AD, the GA is fragmented and atrophic in a population of neurons without NFTs. This lack of correlation between NFTs and fragmentation of the GA is not surprising, given that a similar lesion of the GA has been observed in neurons and other cells in conditions other than AD. Fragmentation of the GA has been, in fact, documented in amyotrophic lateral sclerosis (ALS),[27] in transgenic mice expressing one of the mutations in Cu,Zn superoxide dismutase (SOD) discovered in familial amyotrophic lateral sclerosis,[28] and, experimentally, in cells treated with microtubule depolymerizing agents.[29]

The observation of a fragmented and atrophic GA may be significant for the pathogenesis of AD, because many axonal and presynaptic terminal proteins are processed through the organelle, and they are transported via the fast component of axoplasmic flow.[30] Furthermore, a recent study of the intracellular trafficking of βAPP has disclosed a prominent association of this protein with Golgi elements and with medium-sized, invaginated vesicles in both dendrites and axons.[31] In addition, when primary cultures of rat hippocampal neurons were treated with brefeldin A, a fungal metabolite which produces a redistribution of proteins of the GA into endoplasmic reticulum (ER), with a block in protein transport, the distribution of βAPP immunoreactivity changed, indeed, from Golgi elements to a distribution more characteristic of the ER. In keeping with these findings, immunoblot analysis showed inhibition of βAPP secretion and accumulation of full length βAPP, thus supporting a crucial role for the GA in βAPP maturation and processing.[31] These studies support earlier findings by Haass et al[14] which implicated the GA in the processing of Aβ as well. As previously mentioned, these authors found that Aβ could be released after normal processing of the precursor protein in tissue culture cells, because it was found together with other related peptides in the medium of cells transfected with cDNAs coding for βAPP. Importantly, they also showed inhibition of Aβ generation in cultures treated with brefeldin A, thus implicating the transport of the precursor protein through the GA as a necessary step for the production of Aβ. By pharmacologically manipulating the system these authors determined that the production of Aβ and other fragments is dependent on an acidic environment. Lysosomes, however, did not appear to play an important role in this system, whereas data suggest the existence of an alternative secretory cleavage that could take place in late Golgi vesicles.[14]

The GA, therefore, has been recognized for its central role in the formation of both precursor protein and its soluble fragments, including Aβ. In this context, the results of the study by Stieber et al[1] raise the intriguing possibility that atrophy and malfunction of the GA may precede and/or cause the accumulation of the Aβ peptide. These results correlate with previous findings suggesting that the characteristic lesion in aging and AD is neuronal atrophy rather than degeneration caused by NFT.[25]

This hypothesis, linking a putative malfunction of the GA with accumulation of Aβ, is consistent with a recent *in vitro* observation by Xu et al,[32] who tested one important pathway of βAPP cleavage through the formation of secretory vesicles from *trans*-Golgi network. It was already known that activated protein kinase C (PKC) stimulates the pathway leading to soluble APP instead of its potentially amyloidogenic fragments.[33] Since most βAPP codistributes with a marker of the *trans*-Golgi network, these authors explored the possibility that PKC could redistribute βAPP from the *trans*-Golgi environment to the post-Golgi vesicular compartment where it could undergo processing. They found that activation of endogenous PKC increases the formation of secretory vesicles containing APP from the *trans*-Golgi network, thus implicating important regulatory influences on the normal secretory pathway of βAPP, which involves the Golgi apparatus.[32] These results correlate with genetic studies outlined earlier. Among the families with mutations in the βAPP gene, a Swedish family showed an abnormally high proportion of βAPP being processed through the amyloidogenic pathway, thus producing abnormally high levels of Aβ protein.[34,35] These abnormal levels could be normalized *in vitro* by activation of PKC, which shifts the processing of βAPP toward the non-amyloidogenic pathway.[36] These studies again implicate a role for the *trans*-Golgi pathway in the normal processing of the protein.

A very recent discovery by Sherrington et al[37] adds further support to a possible primary role of the GA in the pathogenesis of AD. These authors have shown a linkage between a very aggressive form of

AD and chromosome 14q24.3. One of the genes isolated from this region, designated *S182*, encodes a protein with seven transmembrane domains, in which five different nucleotide changes were consistently found in seven pedigrees with a particularly aggressive form of early-onset AD. Interestingly, members of the same families without AD, and numerous nonrelated normal individuals, never showed any of those missense mutations. The product of this gene has striking similarities to the *Caenorhabditis elegans* sperm integral membrane protein SPE-4, which appears to be involved in the formation of a specialized Golgi-derived organelle during spermatogenesis in this worm. Such organelle appears to be involved in transport and storage of polypeptides, both soluble and membrane-bound. The corresponding S-182 protein is likely to have similar functions and it could be involved, eg, in the transport and budding of membrane-bound vesicles during transit in the GA.[37] The authors speculate that mutations in this protein could hamper both transport and processing of βAPP, as well as cause abnormal interactions with other proteins such as tau. It would be interesting indeed to study the GA in neurons and other cells from these patients.

Another issue raised again by this paper is a possible link between FGF and AD. MG-160, the integral membrane glycoprotein of the GA, against which antibodies used in this paper were raised, binds to basic FGF (bFGF; reviewed in ref. 38). The GA, therefore, may be involved in regulatory and secretory functions for endogenous bFGF. Although Stieber et al[1] have not succeeded in showing accumulation of endogenous FGFs in NFTs and amyloid deposits, other authors have documented binding of bFGF to neuritic plaques and extracellular NFTs.[39,40] Early functional alterations of the GA, as shown by its atrophy and fragmentation, could be responsible for the abnormal processing and regulation of FGF, resulting in its abnormal deposition. The role of FGFs in AD deserves further study, because, if indeed FGFs are sequestered by NFTs and amyloid plaques, neurons may be deprived of important trophic support.

The paper by Stieber et al[1] raises two questions which may be answered when valid animal models of AD become available. The first question is whether neurons with fragmented GA eventually develop NFTs, or whether these are separate and unrelated pathogenetic mechanisms. The second question is whether neurons with fragmented GA have indeed a defect in their ability to process βAPP and if this could be responsible for the elevated levels of the β-amyloid peptide. Additional insights into the etiology and pathogenesis of AD may be gained if the disease is analyzed from the perspective of the Golgi apparatus and its multiple functions. As succinctly stated by Farquhar and Palade,[21] the Golgi apparatus complex is at the center stage of the cell.

References

1. Stieber A, Mourelatos Z, Gonatas, NK: In Alzheimer's Disease the Golgi apparatus of a population of neurons without neurofibrillary tangles is fragmented and atrophic. Am J Pathol, 1996, 148:415–426
2. Trojanowski JQ, Schmidt ML, Shin R-W, Bramblett GT, Rao D, Lee VM-Y: Altered tau and neurofilament proteins in neurodegenerative diseases: implication for Alzheimer's disease and Lewy body dementias. Brain Pathol 1993, 3:45–54
3. Trojanowski JQ, Lee VM-A: Phosphorylation of neuronal cytoskeletal proteins in Alzheimer's disease and Lewy body dementias. Ann NY Acad Sci 1994, 747:92–109
4. Matsuo ES, Shin R-W, Billingsley ML: Van deVoorde A, O'Connor K, Trojanowski JQ, Lee VM-Y: Biopsy-derived adult human brain tau is phosphorylated at many of the same sites as Alzheimer's disease paired helical filament tau. Neuron 1994, 13:989–1002
5. Shin R-W, Lee VM-Y, Trojanowsky JQ: Aluminum modifies the properties of Alzheimer's disease PHF tau proteins *in vivo* and *in vitro*. J Neurosci 1994, 14:7221–7223
6. Perry G, Siedlak SL, Richey P, Kawai M, Cras P, Kalaria RN, Galloway PG, Scardinia JM, Cordell B, Greenberg BD, Ledbetter SR, Gambetti P: Association of heparan sulfate proteoglycan with the neurofibrillary tangles of Alzheimer's disease. J Neurosci 1991, 11:3679–3683
7. Glenner GG, Wong CW: Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. Biochem Biophys 1984, 120:885–890
8. Haass C, Selkoe DJ: Cellular processing of β-amyloid precursor protein and the genesis of amyloid β-peptide. Cell 1993, 75:1039–1042
9. Selkoe DJ: Cell biology of the amyloid β-protein precursor and the mechanism of Alzheimer's disease. Annu Rev Cell Biol 1994, 10:373–403
10. Wisniewski T, Ghiso J, Frangione B: Alzheimer's disease and soluble Aβ. Neurobiol Aging 1994, 15:143–152
11. Seubert P, Vigo-Pelfrey C, Esch F, Lee M, Dovey H, Davis D, Sinha S, Schlossmacher M, Whaley J, Swindlehurst C, McCormack R, Wolfert R, Selkoe D, Lieberburg I, Schenk D: Isolation and quantification of soluble Alzheimer's β-peptide from biological fluids. Nature 1992, 359:325–327
12. Shoji M, Golde TE, Ghiso J, Cheung TT, Estus S, Shaffer LM, Cai X-D, McKay DM, Tintner R, Frangione B, Younkin SG: Production of the Alzheimer's amyloid β-protein by normal proteolytic processing. Science 1992, 258:126–129

13. Busciglio J, Gabuzda DH, Matsudaira P, Yankner BA: Generation of β-amyloid in the secretory pathway in neuronal and non-neuronal cells. Proc Natl Acad Sci USA 1993, 90:2092–2096
14. Haass C, Hung AY, Schlossmacher MG, Oltersdorf T, Teplow DB, Selkoe DJ: Normal cellular processing of the β-amyloid precursor protein results in the secretion of the amyloid β peptide and related molecules. Ann NY Acad Sci 1993, 695:109–116
15. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, Roses AD: Apolipoprotein E: high-avidity binding to β-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer's disease. Proc Natl Acad Sci USA 1993, 90:1977–1981
16. Saunders AM, Strittmatter WJ, Schmechel D, St. George-Hyslop PH, Pericak-Vance MA, Joo SH, Rosi BL, Gusella JF, Crapper-MacLachlan DR, Alberts MJ, Hulette C, Crain B, Goldgaber D, Roses AD: Association of apolipoprotein E allele E4 with late onset familial and sporadic Alzheimer's disease. Neurology 1993, 43:1467–1472
17. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Perikac-Vance MA: Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993, 261:921–923
18. Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmechel DE, Gaskell PC, Jr, Rimmler JB, Locke PA, Conneally PM, Schmader KE, Small GW, Roses AD, Haines JL, Pericak-Vance MA: Apolipoprotein E type 2 allele decreases the risk of late-onset Alzheimer's disease. Nat Genet 1994, 7:180–184
19. Wisniewski T, Frangione B: Apolipoprotein E: a pathological chaperon protein in patients with cerebral and systemic amyloid. Neurosci Lett 1992, 135:235–238
20. Strittmatter WJ, Weisgraber KH, Goedert M, Saunders AM, Huang D, Corder EH, Dong L-M, Jakes R, Alberts MJ, Gilbert JR, Han S-H, Hulette C, Einstein G, Schmechel DE, Pericak-Vance MA, Roses AD: Hypothesis: microtubule instability and paired helical filament formation in the Alzheimer disease brain are related to apolipoprotein E genotype. Exp Neurol 1994, 125:163–171
21. Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, Katzman R: Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol 1991, 30:572–580
22. Arriagada PV, Growdon JH, Hedley-White ET, Hyman BT: Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology 1992, 42:631–639
23. Farquhar MG, Palade G: The Golgi apparatus (complex) (1951–1981): from artifact to center stage. J Cell Biol 1981, 91:77s–103s
24. Lucassen PJ, Ravid R, Gonatas NK, Swaab DF: Activation of human supraoptic and paraventricular nucleus neurons with aging and in Alzheimer's disease as judged from increasing size of the Golgi apparatus. Brain Res 1993, 632:105–113
25. Salehi A, Lucassen PJ, Pool CW, Gonatas NK, Ravid R, Swaab DF: Decreased neuronal activity in the nucleus basalis of Meynert in Alzheimer's disease as suggested by the size of the Golgi apparatus. Neuroscience 1994, 4:871–880
26. Salehi A, Ravid R, Gonatas NK, Swaab DF: Decreased activity of hippocampal neurons in Alzheimer's disease is not related to the presence of neurofibrillary tangles. J Neuropathol Exp Neurol 1995, 54:704–709
27. Mourelatos Z, Yachnis A, Rorke L, Mikol J, Gonatas NK: The Golgi apparatus of motor neurons in amyotrophic lateral sclerosis. Ann Neurol 1993, 33:608–615
28. Dal Canto MC, Gonatas NK, Chiu AY, Gurney ME: Neuropathological changes in two lines of mice carrying a transgene for mutant Cu,Zn SOD, and in mice overexpressing wild-type human SOD. A model of familial amyotrophic lateral sclerosis (FALS). J Neuropathol Exp Neurol 1995, 54:442
29. Mourelatos Z, Adler H, Hirano A, Donnenfeld H, Gonatas JO, Gonatas NK: Fragmentation of the Golgi apparatus of motor neurons in amyotrophic lateral sclerosis revealed by organelle-specific antibodies. Proc Natl Acad Sci USA 1990, 87:4393–4395
30. Hammerschlag R, Stone GC, Bolen FA, Lindsey JD, Ellisman MH: Evidence that all newly synthesized proteins destined for fast axonal transport pass through the Golgi apparatus. J Cell Biol 1982, 93:568–575
31. Caporaso GL, Takei K, Gandy SE, Matteoli M, Mundigl O, Greengard P, De Camilli P: Morphologic and biochemical analysis of the intracellular trafficking of the Alzheimer's β/A4 amyloid precursor protein. J Neurosci 1994, 14:3122–3138
32. Xu H, Greengard P, Gandy S: Regulated formation of Golgi secretory vesicles containing Alzheimer β-amyloid precursor protein. J Biol Chem 1995, 270:23243–23245
33. Caporaso GL, Gandy SE, Buxbaum JD, Ramabhadran TV, Greengard P: Protein phosphorylation regulates secretion of Alzheimer β/A4 amyloid precursor protein. Proc Natl Acad Sci USA 1992, 89:3055–3059
34. Citron M, Oltersdorf T, Haass C, McConlogue L, Hyng AY: Mutation of the β-amyloid precursor protein in familial Alzheimer's disease increases β-protein production. Nature 1992, 360:672–674
35. Citron M, Vigo-Pelfrey C, Teplow DB, Miller C, Schenk D, Johnston J, Winblad B, Venizelos N, Lannfelt L, Selkoe DJ: Excessive production of amyloid β-protein by peripheral cells of symptomatic and presymptomatic patients carrying the Swedish familial Alzheimer's disease mutations. Proc Natl Acad Sci USA 1994, 91:11993–11997
36. Felsenstein KM, Ingalls KM, Hunihan LW, Roberts SB: Reversal of the Swedish familial Alzheimer's disease mutant phenotype in cultured cells treated with phorbol 12,13-dibutyrate. Neurosci Lett 1994, 174:173–176

37. Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesque G, Ikeda M, Chi H, Lin C, Li C, Holman K, Tsuda T, Mar L, Foncin J-F, Bruni AC, Montesi MP, Sorbl S, Rainero I, Pinessi L, Nee L, Chumakov I, Pollen D, Brookes A, Sanseau P, Polinsky RJ, Wasco W, Da Silva HAR, Haines JL, Pericak-Vance MA, Tanzi RE, Roses AD, Fraser PE, Rommens JM, St. George-Hyslop PH: Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature 1995, 375:754–760
38. Gonatas NK: Contributions to the physiology and pathology of the Golgi apparatus. Am J Pathol 1994, 145:751–761
39. Kato T, Sasaki H, Katagiri T, Sasaki H, Koiwai K, Youki H, Totsuka S, Ishii T: The binding of basic fibroblast growth factor to Alzheimer's neurofibrillary tangles and senile plaques. Neurosci Let 1991, 122:33–36
40. Siedlak SL, Cras P, Kawai M, Richey P, Perry G: Basic fibroblast growth factor binding is a marker for extracellular neurofibrillary tangles in Alzheimer's disease. J Histochem Cytochem 1991, 39:899–904