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Aneuploidy, chromosomal missegregation, and cell cycle reentry in Alzheimer's disease

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Alzheimer's disease (AD) is a neurodegenerative disorder with a complex etiology and pathogenesis. Chromosome missegregation was proposed two decades ago to be responsible for neurodegeneration in AD patients. It was speculated that the aneuploidy is a result of aberrant cell cycle of neuronal progenitors during adult neurogenesis and/or of mature neurons. There is mounting evidence of increased rate of general aneuploidy and cell cycle reentry in the AD patients' brains, with area-specific pattern. In this review, we discuss the involvement of chromosome instability, genome damage and cell cycle impairment in AD pathology.

Key words: Alzheimer's disease, Down's syndrome, chromosome missegregation, genome instability, aneuploidy, cell cycle, apoptosis, oxidative stress, DNA damage, DNA repair, neuron, presenilin

ALZHEIMER'S DISEASE – A COMPLEX AND MULTIFACTORIAL DISORDER

Alzheimer's disease (AD) is a complex, progressive, and irreversible neurodegenerative disease of the brain, and the most common form of dementia in the elderly (Zekanowski et al. 2004). Symptoms start when neurons in brain regions involved in memory, cognition and neurogenesis are being damage and ultimately die. Senile plaques (SPs) and neurofibrillary tangles (NFTs) are the hallmarks of the disease. SPs occur outside neuron bodies, and are composed mainly of beta amyloid peptides (Aβ) produced within neurons, and secreted as a soluble mono- or oligomers. The toxic Aβ is a product of abnormal processing of APP protein (amyloid precursor protein), coding by the *APP* gene located on chromosome 21q21. The second histopathological hallmark of AD, neurofibrillary tangles, are formed of the microtubule-associated protein tau (MAPT), coded by *MAPT* gene located on chromosome 17q21.1. Contrary to SPs, NFTs are located inside neurons.

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Amyloid plaques and neurofibrillary tangles accumulate in the brain and both contribute to the neuronal cell death. However, neither SPs nor NFTs are absolute signs of AD since *post-mortem* brain examinations of some cognitively healthy aged individuals showed both SPs and NFTs (Jellinger and Bancher 1998, Nussbaum and Ellis 2003).

The mechanisms of neurodegeneration in Alzheimer's disease are poorly understood. Both genetic and environmental factors play an important role in AD etiology (Pastor and Goate 2004, Wu et al. 2008). Rare cases of familial AD (FAD) appear to mimic closely the common, sporadic form of the disease (SAD). The majority of FAD cases are caused by mutations in presenilin 1 gene (*PSEN1*). Less common are mutations in two other genes, coding for presenilin 2 (*PSEN2*), and for amyloid precursor protein (*APP*). Epidemiological studies suggest that the *APP* and presenilins' mutations together account for a fairly small proportion of the cases of the early onset disease, even among those designated as the "familial" (Cruts and Van Broeckhoven 1998). Additionally, in few cases mutations in *MAPT* gene caused AD clinical phenotype (Larner 2008). However, there are reports showing the existence of affected large families lacking mutations in the known

causative genes. This suggests that all simple pathogenic loci have been identified, and that other familial clustering is more likely to be oligogenic or epigenetic rather than monogenic in etiology (Bertram and Tanzi 2008). Similarly twin studies showed concordance rate of 58–78%, indicating the impact of epigenetic and developmental risk factors (Gatz et al. 2006).

FAD is used as a model for SAD, and analysis of FAD mutations greatly enhanced the understanding of AD common pathophysiological mechanisms. Nevertheless, it still remains an unanswered question, what is the mechanism of amyloid formation in SAD, other than mutations in the causative genes.

AMYLOID CASCADE HYPOTHESIS AND BEYOND

APP is a transmembrane protein, sequentially cleaved by membrane-anchored secretases. One pathway, non-amyloidogenic, involves α-secretase, which cleaves APP and releases extracellular N-terminal fragment of APP, preventing formation of Aβ. The second, amyloidogenic pathway involves β-secretase cleavage followed by γ-secretase, generating extracellular $A\beta_{1\text{-}40}$, $A\beta_{1\text{-}42}$, and $A\beta_{1\text{-}43}$. The active site of γ-secretase complex encompasses presenilin 1 or presenilin 2. The short version of Aβ is the most common form of the Aβ peptide (90%) and is less amyloidogenic when compared to the longer forms. $A\beta_{1\text{-}42}$ or $A\beta_{1\text{-}43}$ are less soluble and more neurotoxic and tend to aggregate rapidly to form amyloid deposits (Tagami et al. 2008, Trześniewska et al. 2008). Additionally, there are data that Aβ is mitogenic for glial cells and neurons *in vitro* (McDonald et al. 2008).

The transmembrane Notch receptor is similarly cleaved by α- and γ-secretases, which release the Notch intracellular domain (NICD), similarly as the amyloid precursor protein intracellular domain (AICD) is released from APP. NICD regulates transcription of numerous genes. NICD- and AICD localize to the same nuclear transcription compartments making a cross-talk between APP and Notch signaling pathways probable (Konietzko et al. 2008, Słomnicki and Leśniak 2008). In addition, Aβ-like soluble peptide can be cleaved from Notch by γ-secretase (Okochi et al. 2006).

The increased production of $A\beta_{42}$ is probably an important element of the pathogenic process in AD, however, the ultimate causes of the pathology remain still unsolved. According to the amyloid hypothesis, accumulation of $A\beta_{42}$, mainly in hippocampus and cerebral cortex, is the primary pathogenic process, which triggers a cascade of various physiological events such as microglial and astrocytic activation, oxidative damage, formation of tau pathology, synaptic loss and progressive cognitive decline (Lee et al. 2007). The primary neurotoxic factor are most probably soluble Aβ oligomers which bind to numerous cell elements, initiating oxidative damage to membrane lipids, making some of them (like cholesterol) neurotoxic (Chiang et al. 2008, Rauk 2008). Binding of Aβ oligomers to MAPT, and to several protein kinases, results in the hyperphosphorylation of MAPT and abrogation of its microtubule-supporting role in maintaining axon and dendric structure, as well as mitotic spindle structure. Further, it has been suggested that long-term potentiation (LTP), the key element in memory and learning, is particularly sensitive to Aβ oligomers and that Aβ can induce demyelination and oligodendrocyte injury *in vivo*.

However, the amyloid cascade hypothesis is still controversial (Korczyn 2008). For instance, studies on transgenic mice suggest that synaptic dysfunction, including LTP, precedes the formation of plaques and tangles indicating that the histopathological lesions of AD develop after irreversible neuronal damage has occurred (Knobloch et al. 2007). Also, there is a weak correlation between the distribution of Aβ in the brain and the degree of dementia (Thal et al. 2002). Thus, while Aβ is certainly involved in the disease, its generation is probably not an initiating event but rather secondary one to other pathogenic processes, like interruption of neurotrophic signaling. It was recently proposed that the amyloidogenic pathway is activated *in vitro* in the hippocampal neurons as a result of interruption of signaling involving nerve growth factor (NGF) and/or brain derived neurotrophic factor (BDNF) (Matrone et al. 2008). Additionally, Aβ released into culture medium induces increase of APP and PS1 levels, creating a positive feedback.

Several lines of evidence indicate that disturbed maintenance and segregation of chromosomes, DNA damage and impaired repair could lead to altered gene dosage and gene expression, resulting in the cell cycle reentry of postmitotic neurons, as well as of neural stem cells, leading to their death and contributing to AD (Yang and Herrup 2007, Zhu et al. 2007, Boeras et al. 2008). Hypothesis on the role of the cell cycle and

genome stability deregulation unifies all AD pathological elements, including AD causative factors (presenilin mutations, oxidative stress, and chromosomal missegregation), proteins involved in AD (Aβ, MAPT), as well as AD histopathology (Webber et al. 2005).

DOWN'S SYNDROME, LOW-LEVEL MOSAICISM AND ALZHEIMER'S DISEASE

One of the hypotheses, proposed more than two decades ago, links AD and Down's syndrome (DS) (Potter 1991). It is well known that DS patients at the age above 30 years develop brain pathology that is histologically indistinguishable from AD (Wisniewski et al. 1988, Petronis 1999, Stanton and Coetzee 2004). In more than 50% of DS patients over 50 years of age, cognitive impairment progresses to AD like dementia. Synaptic dysfunction could be traced earlier, preceding the motor and cognitive symptoms. For instance, long-term potentiation-like plasticity measured using paired associative stimulation is impaired in DS patients (<40 years of age), as well as in patients with mild-to-moderate AD (Battaglia et al. 2008).

As the *APP* is located on chromosome 21q21, it was proposed that 21 trisomy leads to *APP* overdose and elevated levels of $A\beta_{42}$, which could result in the brain pathology (Oyama et al 1994, Patterson and Costa 2005). As expected, rare *APP* locus duplication, inherited in autosomal dominant manner, cause typical AD angiopathy (Rovelet-Lecrux et al. 2006, Blom et al. 2008). Moreover, in a case study on a DS patient with partial chromosome 21 trisomy outside the *APP* locus no AD phenotype was observed, indicating that *APP* is AD related (Prasher et al. 1998).

It was therefore proposed that late-onset SAD could be a result of developmental deficiencies in chromosome segregation (with genetic or environmental causes), giving rise to aneuploid neuronal progenitors and resulting in low-number (mosaic) chromosome 21 trisomy (Potter 2008).

Aneuploidy, especially chromosome 21 trisomy, seems to affect AD pathophysiology through different mechanisms (Mrak and Griffin 2004). An increased production of amyloidogenic $A\beta_{42}$ caused by overexpression of APP due to the presence of three copies of chromosome 21 is the major candidate for the early onset of AD in DS patients. Indeed, there are data showing that DS patients produce more $A\beta_{42}$, which could be a result of abnormal processing of APP, but also a direct effect of apoptosis (Teller et al. 1996, Galli et al. 1998). In turn, apoptotic stimulus could be more effective in aneuploidic cells, as shown in cortical neurons from DS fetuses, and in aneuploidic neurons from AD patients (Busciglio and Yankner 1997, Herrup et al. 2004). It was also reported that transgenic mice overexpressing APP display enhanced expression of mitochondrial and apoptosis-related genes, as well as reduced expression of genes essential for synaptic plasticity and memory formation (Dickey et al. 2003, Reddy et al. 2004). Also DS mouse models, with duplication of mouse ortholog of human chromosome 21 or knock-in human chromosome 21, display features resembling AD (O'Doherty et al. 2005, Gimenez-Llort et al. 2007, Salehi et al. 2007). It is also possible that other genes located on chromosome 21 can influence neurogenesis and cause neurodegeneration. For instance it was recently shown that additional copy of human chromosome 21 causes inhibition of neuroectodermal differentiation (INDI) of pluripotent mouse ES cells (Mensah et al. 2007). This effect depends on less than third part of genes in two chromosomal regions, located outside *APP* locus (21q11.2-q21.1 and 21q22.2-q22.3). It was also shown that in DS fetuses, and in Ts65DN mice brain regions connected with neurgenesis cell proliferation is impaired and decreased (Contestabile et al. 2007). This could substantially reduce the proliferation potential in the brain and result in size reduction, observed in DS adults.

Numerous epidemiological observations make the hypothesis linking 21 trisomy and AD feasible. The original suggestion springs from studies showing a statistically significant overrepresented DS cases in families with AD, as well as AD cases in families with DS children (Heston et al. 1981, Whalley et al. 1982, Heyman et al 1983, Van Duijn et al 1994). Additionally, some SNPs located within *PSEN1* and associated with AD risk, were also associated with DS (Petersen et al. 2000, Lucarelli et al. 2004). Moreover, a general hyperdiploidy was observed in the cells of the mothers of DS children, which could result both in DS (*via* gonadal trisomy or meiotic non-disjunction), as well as in AD (*via* mosaicism in the brain), developed by the mothers later in life (Staessen et al. 1983).

It was shown that young (<35 years of age) mothers of DS children have a predisposition for chromosomal nondisjunction and could be mosaic for trisomy 21 (Migliore et al. 2006). This causes a five-fold greater risk of developing late onset AD, as compared to gen-

eral population or to a group of older mothers of DS children (Schupf et al. 2001, Schupf et al. 1994). Data presented by Migliore and others (2006) showed a statistically significant increase in micronucleated lymphocytes in the group of young mothers of DS children, as compared to the controls. Micronuclei formation is a well-established marker of chromosome malsegregation and genome instability, and indeed fluorescent *in situ* hybridyzation (FISH) analysis of chromosome 13 and 21 demonstrated increased non-disjunction.

There are several case reports indicating that low-level mosaicism for trisomy 21 results in AD-like dementia (Rowe et al. 1989, Hardy et al. 1989, Percy et al. 1991). Early studies confirmed also increased levels of aneuploidy and small chromosomal rearrangements in AD patients (Ward et al. 1979, Nordenson et al. 1980, Buckton et al. 1983, Migliore et al. 1997, 1999). It should be noted that low-level chromosome 21 trisomy is not sufficient to cause full, systemic Down's syndrome phenotype.

Analysis of cultured fibroblasts and leukocytes from SAD and FAD patients with *PSEN1* and *APP* mutations revealed an increase in aneuploidy level, with no correlation with age or gender, in comparison to cells from control subjects (Migliore et al. 1997, 1999, Geller and Potter 1999). Observations using classical cytogenetic approach gave ambiguous results, mainly because of limited ability to detect low level mosaicism, as well as low number of metaphases examined. These difficulties were overcome using FISH method, allowing detection of chromosomal rearrangement also in the interphase nuclei. Recently a mosaicism for trisomy 21 was detected using FISH in a young patient with a diagnosed early-onset AD (Ringman et al. 2008). The authors postulated that FISH screening for mosaicism should be indicated in selected patients with mild developmental delay, and those with AD of early onset.

Aneuploidy does not seem to be a primary event in AD pathology, but rather a secondary one, which in turn leads to changes in *APP* expression and/or its processing, as well as to apoptosis. It is suggested that the same mechanism leads both to DS and to late-onset AD. The predisposition to chromosome missegregation could result in mosaicism at meiotic level (in germ cells), as well as at mitotic level (e.g. in lymphocytes and in the brain). It could be suggested that the rate of pathological processes is much slower in sporadic AD than in DS, due to the low level of trisomy in neurons and in glial cells.

The influence low-level aneuploidy could be modulated by a common polymorphism of apolipoprotein E gene (*APOE*). *APOE* encode three protein isoforms (ε2, ε3, ε4). Allele *APOE4* coding for ε4 is the only well-established risk factor for AD. It was suggested that ε4 isoform promotes polymerization of Aβ into oligomers and amyloid filaments (Potter et al. 2001). Moreover, APOE protein facilitates proteolytic clearance of soluble Aβ from the brain, enhancing degradation of Aβ within microglia by neprilysin and related enzymes (Jiang et al. 2008). APOE isoforms differ in their effectiveness of Aβ clearance enhancement (ε2 > ε3 > ε4). Additionally, specific binding of ε4 to microtubule-associated proteins may interfere with microtubule function and possibly influences mitotic spindle formation. This can results in the observed significantly higher proportion of *APOE4*/*APOE4* genotype among young mothers of Down's syndrome children, and with the second meiotic division error (Strittmatter and Roses 1995, Avramopoulos et al. 1996, Ezquerra et al. 1998). The apolipoprotein example shows that the same protein could interact with classical amyloid cascade, and at the same time influence genomic stability, which in turn could enhance amyloid cascade.

NEUROGENESIS AND ANEUPLOIDY IN THE BRAIN

The influence of neurogenesis in the adult brain on above-mentioned mosaicism in AD seems to be complicated. Previous studies indicated that the overall aneuploidy frequency is ca. 10%, which is equivalent to 0.1–0.7% per sister chromosomes in an adult, healthy human brain (Iourov et al. 2006). In the fetal brain overall frequency is 2–3 times higher, and it is postulated that programmed cell death can be directly connected with removal and quality control of aneuploid cells (Yurov et al. 2007). The aneuploidic neurons were shown to be functionally active, resulting in heterogenous gene expression in mixed euploid and aneuploid cell population (Kingsbury et al. 2005). This imposes either physiological advantage or – probably more frequently – neurodegeneration (Yurov et al. 2008). Chromosomal imbalance was connected not only with AD, but also with other mental disorders like schizophrenia and autism (Vorsanova et al. 2007, Yurov et al. 2008).

It should be noted that general mosaicism could be more prevalent than it was previously believed. Direct estimation of the rate of mosaic carriers in the

population is not feasible at present, especially for cryptic mosaicism due to non-disjunction in second meiotic division (Kovaleva 2007). There are also suggestions that a large proportion of asymptomatic mosaics originated from normal diploid zygote by a mitotic error (Richards 1974).

Neurogenesis has some regenerative potential but on the other hand it could also produce more aneuploidic stem cells, as well as progenitors with limited self-renewal ability, in individuals who have a predisposition to missegregation. Indeed, the pathogenic processes of AD start from the regions of the highest neuronal plasticity and the regions involved in neurogenesis (Arendt et al. 1998). The expression of the cell cycle markers and the markers of immature neuronal cells could suggest also enhanced neurogenesis in AD patients' brains. Consistently, neurogenesis was enhanced in the brains of transgenic mice with APP mutation (Jin et al. 2004). The technical problem remains, how the pathogenic generation of aneuploidic cells (or cells with incomplete cell cycle) could be distinguished from neurogenesis generating functional neurons. The solution could be the simultaneous tracing of cell cycle markers, FISH markers and DNA synthesis (Taupin 2008).

Aneuploidy was observed also in the brains of FAD cases (Yang et al. 2001, Mosch et al. 2007). Data presented so far indicated that 4–10% of the neurons in the regions of amyloid lesions are aneuploid. This is in agreement with the results, showing that in AD hippocampus there is 3–4% of aneuploid pyramidal neurons (Yang et al. 2001). Recently, increased aneuploidy of chromosome 17 and 21 has been also observed in buccal cells of AD patients, as well as in aged subjects over 64 years (Thomas and Fenech 2008). The same authors, however, demonstrated no increase in the aneuploidy rate in hippocampal area of AD patients.

A considerable degree of hyperploidy in normal adult brains has been detected using FISH to sorted isolated nuclei (Rehen et al. 2005, Yurov et al 2005). According to Mosch and colleagues (2007) the number of overdiploid (>2n) neurons in the normal brains could reach 6–12%. This result corresponds to the rate of hyperploidy per individual chromosome between 0.1% and 0.8%, as determined previously. These neurons do not express markers of the cell cycle (e.g. cyclin B1), so did not re-enter the cell cycle and could be classified as constitutional tetraploidy (static population) resulting from mitotic chromosomal missegregation in neuronal progenitor cells (Yang et al. 2003). In the brains of AD patients the number of >2n neurons is increased up to 20%. Contrary to controls, the majority of AD hyperploid neurons express cyclin B marker of the cell cycle ("cycling neurons"), indicating that they reentered the cell cycle and at least started DNA synthesis (see below). It was proposed that neurons expressing cell cycle markers are particularly vulnerable to apoptosis. The majority of these neurons stay in the S phase. According to Mosch and coauthors (2007) only 1–2% of neurons, which reentered the cell cycle, completed DNA replication. Therefore, a distinction should be made between aneuploid "cycling neurons", and "static neurons". The first population could be potentially involved in neurodegeneration.

In 2008 Iourov and coworkers used a novel technique, allowing analysis of interphase chromosomes integrity (interphase chromosome-specific multicolor banding, ICS-MCB), to assess chromosome 21 aneuploidy in various regions of the brains from AD patients and age-mached controls (Iourov et al 2007, 2008). In each of the brain regions (the cerebral cortex, hippocampus and cerebellum) 15 000 cells were screened separately for AD patients and controls (totally 58 000 cells). In the control samples, the average rate of chromosome 21 aneuploidy was 0.7% with no regional specificity. However, in AD patients brains the average rate of chromosome 21 aneuploidy was substantially higher, achieving 29.3% in hippocampus, 20.7% in cerebral cortex, and 1.7% in cerebellum. The authors proposed that observed aneuploidy results from aberrant adult neurogenesis, affected by mitotic non-disjunction caused by defective cell cycle re-entry. The data confirms an association of area-specific aneuploidy, cell cycle errors during adult neurogenesis, and strongly support cell-cycle hypothesis of AD pathology.

Aberrant neurogenesis leading to generation of novel, aneuploidic neurons and glial cells from neuronal progenitors in the adult brain, could be connected with the pathological function of mutated presenilins. Neurogenesis, which occurs in the adult mammalian and human brains at a reduced rate with advancing age, could be stimulated by physiological and pathological factors (e.g. in AD brains), especially in CA1 hippocampal region (Jin et al. 2004). Neurogenesis is also stimulated in younger age of transgenic mice displaying all AD features. Neurogenesis starts during MAPT hypherphosphorylation, which precedes cell

cycle, apoptosis and neurodegeneration (Schnidowski et al. 2008). This suggests that aberrant neurogenesis process leading to aneuploidic neurons could cause chromosomal missegregation and apoptosis later in life.

With the rate of neurogenesis reaching ca. 1–2 000 novel neurons per day, it could be speculated that the amount of resulting aneuploidic cells should be sufficient to cause a phenotypic effect after decades. It seems that the newly generated neurons in the dentate gyrus of AD brain do not become mature, although neuroproliferation is increased (Li B. et al. 2008). It is also noted that aneuploidic neurons and the glial cells detected in AD patients produce more Aβ peptides than normal cells (LeBank 1995, Galli et al. 1998). Trisomic glial cells overexpress interleukine-1 and could start the amyloid cascade (Liu et al. 2005, Mrak and Griffin 2005). Indeed, the amyloid cascade hypothesis suggest that the role of glial cells in AD pathology is connected with later events, encompassing inflammatory reaction (interleukin-1 expression) and production of amyloid-promoting proteins (like APOE and antichymotrypsin).

Alzheimer's disease could be the end product of aneuploidic events encompassing chromosome 21 and 17 trisomy, especially in the neuronal progenitors. This mechanism could also be triggered by the $A\beta_{42}$ release from neuronal and glial cells at the initial stage of AD pathology. It could spread and amplify the AD phenotype ("pathocopy") all over the brain. It is also possible that aneuploidy may be a result of the mature neurons cell-cycle re-entry in response to environmental stimuli.

MITOTIC MISSEGREGATION AND PROTEINS INVOLVED IN AD PATHOLOGY

Genomic changes observed in AD include aneuploidy and chromosome missegregation but mechanisms leading to these changes are not clear. One of the possible explanation involves chromosomal missegregation in mitosis during the fetal development, with presenilin proteins as the key player (Potter 2005). Both presenilins (PS1 and PS2) were proposed to colocalize with the nuclear envelope markers, as well as with cytoskeleton associated proteins and microtubules, and to be involved in chromosome organization and movement during the cell cycle (Li J. et al. 1997, Honda et al. 2000, Johnsingh et al. 2000, Pigino et al. 2001). Chromosome missegregation in neurogenesis could then result in low-level aneuploidy in AD brain.

Data from *in vivo* and *in vitro* study of transgenic mice cells expressing mutated *PSEN1* and *APP* constructs revealed a substantial aneuploidy for various chromosomes, which was positively correlated with the age of the mice (Boeras et al. 2008). In case of transgenic mice expressing *PSEN1* wilde-type sequence, the observed trisomy levels observed were more than 2 times lower. Also transiently transfected telomerase-immortalized human mammary epithelial cell line (hTERT-HME1) overexpressing wild type or mutated *PSEN1* constructs showed similar level of general aneuploidy. Similar results were obtained in transgenic mice with one copy of mutated *PSEN1* or *APP* genes, expressing construct in a developmentally proper way (Potter 2008). In addition, various cells transfected with mutated *PSEN1* or *APP* construct or cells isolated from transgenic mice with *PSEN1* or *APP* mutated constructs and incubated with $A\beta_{42}$ or $A\beta_{40}$ peptides develop aneuploidy, especially trisomy of chomosomes 21 and 12 (Potter et al. 2008). Analysis of mitotic apparatus of cells transfected with mutated constructs showed abnormal microtubule arrays and lagging chromosomes, which could lead to dysfunction or disruption of mitotic spindle, chromosomal missegregation, and aneuploidy.

Presenilin 1 (and/or presenilin 2) is a major constituent of γ-secretase active site. It was recently shown that inhibition of γ-secretase complex in human epithelial cells and *APP* knock-out mouse splenocytes *in vitro* induces cell cycle defects and chromosome missegregation (Goodwin et al. 2008). Different inhibitors blocked the cell cycle in G_o and G_2 or generate significant levels of aneuploidy with normal cell cycle progression. Specific inhibitor of APP cleavage (e.g. imatinib mesylate), which leaves Notch cleavage unaffected, also causes significant increase in aneuploidy. This could suggest that inhibition of γ-secretase APP cleavage activity can result in aberrant cell cycle and chromosomal missegregation.

Presenilins influence also other signaling pathways. For instance, PS1 promotes the PI3K/Akt signaling pathway and suppresses caspase-3 activity, as well as dendrite retraction and apoptosis (Baki et al. 2008). Mutated forms of PS1 are unable to activate PI3K/AKT signaling, prevent phosphorylation of GSK-3, and as a result increase its activity, and promote activation of caspase-3. It was shown that GSK-3 plays an important

role in accurate chromosome segregation (Tighe et al. 2007). GSK-3 inhibitors do not prevent G_1/S progression or cell division in HeLa cells. However, they significantly delay mitotic exit, due to difficulty in chromosome alignment, resulting in chromosome missegregation. Specific *PSEN1* mutations could cause increased MAPT protein phosphorylation (*via* GSK-3), and disruption of its ability to associate with cytoskeleton proteins, promoting in turn aggregation of MAPT, and probably influencing mitotic spindle formation (Baki et al. 2004).

GSK-3 phosphorylates numerous other neuronal cell specific microtubule associated proteins, like MAP1 and MAP2, influencing microtubule dynamics (Dehmelt and Halpain 2005). A newly characterized MAP9 protein (ASAP) is essential for cell cycle progression, and its deregulation results in profound defects in mitotic spindle formation and mitotic progression leading to aneuploidy, cytokinesis defects and/ or cell death (Venoux et al. 2008). ASAP is also involved in DNA damage response, another element important in AD patophysiology.

Specific *PSEN1* mutations could block translocation of PS1 to the nuclear envelope (Honda et al. 2000). Based on these observations, Potter (2005) suggests that both PS1 and PS2 could serve as anchors to attach the kinetochores to the inner nuclear membrane during interphase. PS1 and PS2 could help in chromosomal translocation and release during the cell division.

The data suggests that mutated PS1, either directly or *via* different signaling pathways could cause general chromosomal missegregation, not confined to chromosome 21 trisomy. Resulting chromosome 17 aneuploidy could cause over-expression of *MAPT* and progranulin gene (*PGRN1*). The latter is also involved in neurodegenerative disorders like fronto-temporal dementia. Resulting neuronal progenitor cells aneuploidy could influence amyloid cascade, as well as defective mitotic spindle formation.

Other functions of presenilins connected with the cell cycle include their involvement in signaling pathways important for cell cycle regulation, such as β-catenin signaling (Chevallier et al. 2005). Specific *PSEN1* mutation associated with FAD cause destabilization and increased degradation of β-catenin (Zhang et al. 1998, Weihl 1999). This in turn could cause deficiency in β-catenin signaling and impairment of the cell cycle. Specific *PSEN1* mutations, e.g. L166P, not only induce an exceptionally high increase of $A\beta_{42}$ production, but also impair NICD, AICD production as well as Notch signaling (Moehlmann et al. 2002). Notch-1 is expressed primarily during embryogenesis and development; it is also expressed in the adult brain, in regions with high synaptic plasticity, and involved in neurogenesis, and renewal of neuronal stem cells, irrespective of spatial or temporal niche (Alexson et al. 2006, Nagarsheth et al. 2006).

There are other proteins taking part in cell division during the brain development, which are involved in AD pathology. For instance, it was proposed that APP localize to the nuclear membrane and centrosomes in dividing cell (Dranovsky et al. 1996). APP (like MAPT) is phosphorylated during mitosis (Suzuki et al. 1994, Illenberger et al. 1998). Phosphorylation of APP modulates APP processing, resulting in the higher production of $A\beta_{42}$ (Xu et al. 1996).

Aβ induces phosphorylation of other proteins involved in cell cycle events, like pRb, a product of the retinoblastoma susceptibility gene with tumor suppression activity (Ma et al. 2003). pRb is involved in various cellular functions, including cell division, differentiation, apoptosis and senescence. Together with other proteins, hypophosphorylated pRb stops cell cycle, and inhibits expression of cell cycle proteins. Hyperphosphorylated pRb allows expression of E2F target genes and, in result, causes progression of cell cycle through G1 up to M, where pRb becomes again dephosphorylated. It was shown that pRb is hyperphosphorylated and abnormally redistributed to the cytoplasm in AD brains, causing abnormal re-entry of neurons into the cell cycle (Thakur et al. 2008). Then, adult neurons could be stimulated to undergo aberrant mitotic divisions, resulting in aneuploidic progeny (Nagy et al. 1998, McShea et al. 1999). Chromosomal missegregation could result in aneuploidy as well as influence numerous mitosis-specific proteins, especially protein kinases (Suzuki et al. 1994, Herrup et al. 2004). This probably results in hyperphosphorylation of APP and MAPT proteins, affecting mechanisms of amyloid cascade and apoptosis. The ultimate result could be the same as in the case of low level trisomy 21 (Potter 1991).

It was also shown that the microtubule-associated protein CLIP 170, required for centrosome function, binds to PS1 and is essential for γ-secretase activity (Tezapsidis et al. 2003). Moreover, disturbances in mitosis could induce specific localization of presenlilins to centrosome and kinetochore microtubules

(Jeong et al. 2000). Localization of PS1 seems to depend on the age, which could additionally influence AD patophysiology (Kimura et al. 2001). Consistently, it was reported that presenilin mutations could inhibit cell cycle, as well as inhibit binding of cytoskeleton-interacting proteins and microtubule associated proteins (like MAPT) (Janicki and Monteiro 1999, Johnsingh et al. 2000).

MAPT associate with tubulin in the formation of microtubules, which in turn make the cell shaped and structured, and generates cellular transport network. Several observations suggest that axonal and dendritic arrays may be established by mechanisms very similar to mitotic spindle formation. In both processes MAPT plays a vital role, interacting with other microtubule associated proteins (Baas 1999). Hyperphosphorylation of MAPT protein leads to breakdown of the microtubule system, which in turn causes defects in mitotic spindle leading to aneuploidy (Kuhn et al. 2007). Also recent studies using a *Drosophila* tauopathy model showed that tau (wild type and mutant) can cause cell cycle re-entry, depending on hyperphosphorylation (Khurana et al. 2006).

PREMATURE CENTROMER DIVISION AND AD

Another line of evidences suggesting a link between AD and chromosomal missegregation comes from analysis of premature centromer division (PCD) (Spremo-Potparevic et al. 2004). Centromere is a chromosomal region, which helds sister chromatids between the end of replication and the start of segregation, playing a fundamental role in accurate chromosome segregation during meiosis and mitosis. Centromere is also vitally important in microtubule attachment, chromosome movement and mitotic checkpoint control. PCD is connected with a loss of control over separation and segregation of chromosomes, takes part just after centromere replication in the interphase, and results in premature separation of chromatids, leading to aneuploidy in aging, chromosome instabilty syndromes and other diseases (Mehes and Kosztolanyi 2004).

Epidemiological studies suggest that PCD could be more frequent in women with familial AD as compared to age-matched controls (Moorhead and Heyman 1983, Lao et al. 1996). In peripheral blood leukocytes from AD patients, there is a higher percentage of PCD compared to controls (Spremo-Potparevic 2004). Also Zivkovic et al showed that PCD of chromosome 18 is significantly increased in leukocytes of sporadic AD patients, and is correlated to aneuploidy (Zivkovic et al. 2006). These authors also demonstrated an increased hyperploidy and hypoploidy in AD patients, which could be related to chromosome instability, as a result of PCD in interphase nuclei. Recently Spremo-Potparevic and coworkers (2008) showed X chromosome PCD in interphase nuclei of frontal cerebral cortex neurons from sporadic AD patients. The average frequency of PCD in AD patients was almost three times higher than in the control group, and was highly significant. It should be noted that PCD in neural stem cells could result in aneuploid neuronal progeny.

All observations could suggest a loss of timing and control over centromere separation, which could result from defects in microtubule organization, and missegregation of sister chromatides. Cyclin dependent kinase 11 (CDK11) isoforms could play an important role in these processes, as CDK11 can induce putative centromere instability, as well as plays a crucial role in mitotic progression, maintenance of sister chromatids cohesion, completion of mitosis, and in apoptosis (Bajic et al. 2008).

It was also recently proposed that centrosome-associated RNA (cnRNA) could derive from the centrosome independent genome (Alliegro and Alliegro 2008). cnRNA together with paired centrioles and pericentriolar matrix constitute the major microtubule organizing center (centrosome). cnRNA are dynamic molecules, which are transported around cytoplasm in patterns associated with mitotic apparatus and probably play a role in spindle formation. It could be speculated that increased level of nucleic acids damage connected with AD influence functioning of cnRNA more profoundly than DNA, affecting mitotic spindle formation and leading to chromosome missegregation.

It should be stressed that till now no mitotic cells were found in the mature neurons, both in AD and in control brains, suggesting an inherent inability of post-mitotic neurons to divide. In consistency with this view, neuronal PCD could be seen as a result of cell cycle deregulation, leading to neurodegeneration, and cell death mediated probably by the expression of the cell cycle dependent kinase 2 (cdc2) (Konishi and Bonni 2003). Interestingly, cdc2 is overexpressed in AD brains, within neurofibrillary tangles and glia (Vincent et al. 1997).

Taking the data together, it could be hypothesized that presenilin mutations and other pathogenic processes connected with AD progression influence not only the γ-secretase functioning. Also chromosomal organization and interaction with nuclear envelope during interphase, and their detachment from the nuclear envelope during mitosis and/or movement during cell division could be impaired in AD.

CELL CYCLE REENTRY AND DEATH OF AD NEURONS

The eukaryotic cell cycle is one of the fundamental life processes consisting of four functionally distinct phases: G_1 – a period of growth and preparation for replication, S – in which DNA is replicated, G_2 – preparation for mitosis and finally M phase, in which the chromosomes condense and are divided between two daughter cells. Cell cycle progression is governed by two critical classes of proteins – cyclin-dependent kinases (cdks) and their regulatory subunits cyclins. Complexes of cdks and cyclins are master controllers expressed in phase-specific manner and controlled by proteasomal degradation. Their activity is regulated by phosphorylation as well as by a number of cell cycle inhibitors, linking many cellular signaling pathways with the cell cycle machinery. Progression through the cell cycle is based on the control of correct accomplishment of one phase, allowing progress to the next one, known as restriction points (checkpoints). Main checkpoints operate at G_1/S, G_2/M and M/G_1 transition. In case of any cellular damage, especially in DNA, the cell cycle is arrested until the damage is repaired. However, if the damage is too extensive, or repair process not sufficient, cell cycle associated apoptosis is induced and the cell is eliminated.

In the central nervous system (CNS), the cell cycle was known to occur in association with neurogenesis. After neurogenesis, neuroblastomas leave ventricular or subventricular zone and as mature neurons become permanently post mitotic, arrested in G_0 phase. Mature, terminally differentiated neurons in G_0 phase exhibit extremely strong blockade against cell cycle reentry. It is assumed that the blockade is linked with ubiquitine-proteasome degradation pathway of cell cycle molecules (Staropoli and Abeliovich 2005). Another mechanism in quiescent neurons involves strong binding of retinoblastoma (Rb) protein to transcription factors of the E2F family; E2F proteins upon release from Rb drive the expression of a number of genes that initiate the cell cycle (Harbour and Dean 2000). Moreover, the null mutation in Rb gene in tg mouse resulted in massive cell death in the embryonic CNS (Lee E.Y. et al. 1992). This gave rise to the concept linking forced reentry in the cell cycle with cell cycle associated apoptosis. Several further studies, in which DNA replication in mature neurons was demonstrated by incorporation of bromodeoxyuridine (BrdU) into DNA, further substantiated the notion that postmitotic neurons can reactivate replication under stress conditions but that the cell cycle reentry is lethal (Park et al. 2000, Chen et al. 2003, Appert-Collin et al. 2006). In the novel mouse model obtained recently, cell cycle reentry in adult post-mitotic neurons triggered by the loss of functional pRb resulted in progressive neurodegeneration (Lee H. et al. 2008).

The hypothesis that aberrant reactivation of the cell cycle might cause neurodegeneration leading to cell death was proposed more than a decade ago (Arendt 1993, Heintz 1993, Raina et al. 2004). Several studies have reported increased levels and mislocalization of numerous cell cycle proteins in postmitotic neurons located in the hippokampal region of postmortem AD brains. These include cyclin D, E and B, cdk4, cdc2, proliferating cell nuclear antigen (PCNA), and a number of cdk inhibitors, such as p21 and p105 (McPhie et al. 2003, Yang and Herrup 2007). Described cell cycle proteins usually appear only in mitotic cycling cells. Their ectopic activation in AD neurons seems not to be an epiphenomenon of AD, a result of non-specific protein dysregulation, but indeed was accompanied by DNA replication. In brain areas affected by AD, a significant fraction of hippocampal pyramidal and basal forebrain neurons proved to have fully or partially replicated their DNA in four separate genetic loci on few different chromosomes, as demonstrated by FISH to unique specific loci and to the cetromeres of specific chromosomes (Yang Y. et al. 2001). Cells in unaffected AD brain regions or in the hippocampus of nondemented age-matched controls show no such anomalies (Yang Y. et al. 2001). This is in agreement with identification in AD neurons of the cell cycle proteins characteristic for the G_1, S and G_2 phases but not for late mitosis. It suggests that in these neurons G_1/S checkpoint mechanisms fail and neurons are allowed to replicate their DNA and progress to G_2 phase, but than the control of G_2/M checkpoint blocks their cell cycle completion (McShea et al. 2007, Nagy 2007). AD neurons can com-

plete a nearly full S phase, but because mitosis is not initiated, these cells remain aneuploid or tetraploid (Herrup and Arendt 2002). Interestingly, statins widely used in treatment of hypercholesterolemia, that may be beneficial in treating AD, block the cell cycle at G_1/S restriction point (Sala et al. 2008). Incomplete replication could be the effect of DNA damage accumulation and of decreased activity of replication machinery (Lovell et al. 2000, Nouspikel and Hanawalt 2003). In result, these neurons are stuck in abortive cell cycle with the genetic imbalance caused by incomplete DNA replication, what might result in chromosome instability, as discussed earlier in this review.

The question arising from this hypothesis was whether the observed cell cycle reentry was a cause of neurodegeneration and cells death in AD or merely one of late by-products of AD pathogenesis. First suggestion came from the demonstration that the inhibition of the cell cycle proteins such as cdks induces neuroprotective effects (Rideout et al. 2003). Than *in vivo* studies indicated that reentry of postmitotic neurons in the cell cycle and DNA replication is an early event in AD; this notion was based on the description of postmitotic neurons with elevated expression of cell cycle proteins in postmortem brains of patients with Mild Cognition Impairment (MCI) (Yang et al. 2003). MCI is a risk stage for development of AD within next 3–5 years. The percentage of cell cycle positive neurons was similar in MCI and late AD brains. Recently it was proposed that cell cycle events occur in cerebellar dentate nucleus from patients with AD diagnosis, even in the absence of high levels AD hallmarks (Herrup et al. 2008). This could suggest that the early AD pathology is connected with cell cycle events in cerebellum, which is consistent with clinical observations of early AD signs (like motor slowing and other disturbances). Further evidences for causative role of cell-cycle reentry in AD pathogenesis were provided by *in vivo* studies in four different APP transgenic mice models (Yang et al. 2006). In these mice expression of cell cycle proteins and DNA replication occurred several months before first Aβ deposits or microglia activation. This study suggests also that APP transgenic mice models recapitulate signs of the human AD pathology progression in temporal and spatial pattern. However, in none of the transgenic mouse models any significant cell death of neurons occurred. Even in the regions of pronounced AD pathology the calculated rate of neuronal death is 1 in 10 000 per day, indicating that aneuploidic/polyploidic neurons could live for years before they die (Kingsbury et al. 2005). This was surprising and gave basis for the so called two-hit hypothesis, assuming that cell cycle reentry in neurodegeneration is a first event in postmitotic neurons under stress, but is not sufficient to induce apoptosis (Yang and Herrup 2007, Zhu et al. 2007). According to this concept, cell cycle positive neurons are committed to death program, but survive for month until finally a second "hit", i.e. an additional stress factor triggers their death (Fig. 1). Such a convergent model is consistent with chronic nature of neurodegenerative process, characterized by progressive rather than rapid loss of neurons (Yang and Herrup 2007). Moreover, it was suggested that activation of cell cycle proteins by the first "hit" may represent a protective response to stress factors, allowing neurons survive due to additional alleles of genes produced by DNA replication. The price for survival is however appearance of pathological changes characteristic for neurodegeneration. Indeed, it was demonstrated that forced cell cycle reentry in postmitotic neurons by adenoviral mediated expression of c-myc and ras oncogenes led to tau phosphorylation and NFT-like conformational changes typical for AD (McSchea et al. 2007). It seems that in the course of AD a positive feedback loop between different stress factors and cell cycle escalates with time, resulting eventually in neuronal death.

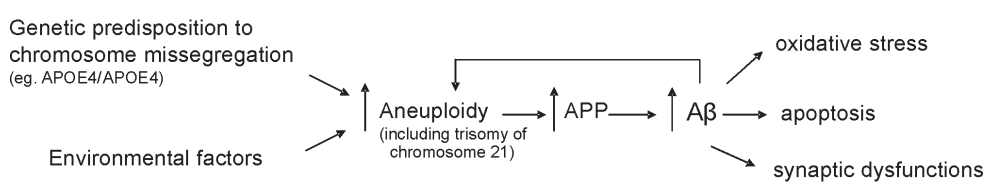

Fig. 1. Relationship between aneuploidy of neural progenitors (during development and in adult brain) and toxic Aβ peptides in Alzheimer's disease and Down's syndrome. Aneuploidy precedes changes in APP expression, such as in case of trisomy of chromosome 21 in DS. It results in an increased level of soluble Aβ oligomers what in turn causes impairment and finally death of neurons. Aβ oligomers can increase aneuploidy level (feedback loop).

The key issue in the cell cycle hypothesis was to identify stimuli which lead from cell cycle activation to neurodegeneration and eventually cell death. This could help to elucidate the relationship between established players in AD such as Aβ and MAPT on one side and on the other side signaling pathways which might be turning on the cell cycle associated death of neurons.

OXIDATIVE STRESS, DNA DAMAGE, Aβ, AND CELL CYCLE ASSOCIATED NEURONAL DEATH

Among mitogenic stimuli which could induce cell cycle activation in postmitotic neurons in AD development, the first suspects were those related to aging, from the group of AD risk factors, including oxidative stress and elevated homocysteine levels (Fig. 1). The important role of oxidative stress in this process was supported by the demonstration that hypoxia-ischemia and stroke are indeed insults which can trigger cell cycle reentry (Kuan et al. 2004, Rashidian et al. 2007, Wen et al. 2007). Oxidative stress and production of reactive oxygen species was one of well established condition inducing DNA fragmentation and damage associated with death by apoptosis (Higuchi 2003). Numerous reports show signs of oxidative damage and DNA breaks in AD brain, such as elevated levels of oxidative damage marker 8-hydroxy-2'-deoxyguanosine (8HdG) and enhanced activity of poly(ADP-ribose) polymerase (PARP), an enzyme induced by the DNA breaks (Love et al. 1999). DNA damage levels in cerebral cortex of AD patients are 2-fold higher compared with controls and were found both in the cortex as well as in lymphocytes of AD patients (Mullaart et al. 1990, Migliore et al. 2005). It is also known that mature neurons in AD are more vulnerable than other cell types to DNA-damaging insults, probably because they are deficient in extensive DNA repair mechanisms that decreased with age (Nouspikel and Hanawalt 2003). In AD brains, levels of free 8HdG, released during repair of DNA, and activity of Mre11 DNA repair complex were significantly lower than in control brains (Love et al. 1999, Mullaart et al. 1990). Interestingly, APOE4 is less effective in protecting neurons from free radicals, and at the same time the most sensitive to free radical damage, compared to other two APOE isoforms (Miyata and Smith 1996). Deficient DNA repair sensitizes neurons and glial cells to oxidative DNA damage, and could enhance generation of double strand breaks (DSBs) (Nagy 2000). Incorrectly repaired DSBs could in turn cause chromosomal rearrangement and general genome instability (Gent et al. 2001). The accumulation of damage in a cell leaves it with an important decision; undergo apoptosis and die, or survive at the cost of living with a modified genome. An increased tolerance to damage can lead to an increased rate of survival with greater accumulation of DNA alternations (Friedberg et al. 2006). Consistently, oxidative stress and DNA damage are known factors contributing to neurodegeneration in AD.

However, direct relationship of DNA damage and incorrect repair to cell cycle associated cell death in AD neurons was not clear. Important progress in this aspect was done by the demonstration that DNA damage in terminally differentiated postmitotic cortical neurons in culture triggered cell cycle reentry and activated a cell death program (Kruman et al. 2004). It was than proposed that cell cycle activation is a critical component of the DNA damage response of postmitotic neurons leading to apoptosis (Kruman et al. 2004). In contrast, apoptosis induced by factors that do not target DNA (staurosporine and colchicine) did not initiate cell cycle activation. The genotoxic agents that induced cell cycle reentry associated and followed by neuronal apoptosis included homocysteine and Aβ, both factors involved in AD pathogenesis. Hyperhomocysteinemia is associated with uracil misincorporation into DNA and chromosomal breakage whereas several pathways were described linking Aβ with DNA damage and apoptosis (Kruman et al. 2002). An obvious candidate protein that might link genetic stress induced by DNA damage and cell cycle reactivation in neurons is p53 transcription factor and tumor suppressor protein. P53 induces DNA repair and, depending on the outcome of the DNA repair, it can activate cell cycle progression or apoptosis. P53 overexpression was reported in cultures exposed to Aβ and in AD brains (Cenini et al. 2008, Uberti et al. 2007, Lanni et al. 2008). $A\beta_{1\text{-}42}$ directly activate p53 promoter (Ohyagi et al. 2005) and at the same time AICD mediates induction of p53 expression, leading to apoptosis (Checler et al. 2007). Moreover, p53 upregulation coincides with cell cycle reentry induced by DNA damage in cultured neurons (Kruman et al. 2004). However, there is a debate whether reactivation of the cell cycle in response to Aβ is p53 dependent in AD.

Proapoptotic function of Aβ is widely recognized, but numerous mechanisms of toxic action have been proposed. Aβ localizes to nucleus where oligomeric Aβ can bind to DNA and cause strand breaks, as well as DNA remodeling (Suram et al. 2007). Structural changes in DNA caused by Aβ could in turn influence numerous processes like replication, transcription, and DNA protection against oxidative stress. Aβ has been also suggested to cause activation of the growth arrest and DNA damage inducible gene (GADD45), implicated in the DNA excision repair. In AD patients' brains there is a correlation between generation of strand breaks and DNA incomplete repair with accumulation of Aβ (Suram et al. 2007). Moreover, Copani and coworkers (2007) showed that in Aβ-intoxicated neurons, DNA polymerase-β is an essential component of the DNA replication machinery, involved at early stages of pathogenesis. These data sustain a strong indication that changes in expression of several DNA repair proteins are associated with Aβ-related pathogenic processes in AD and support the hypothesis of a close association of cell cycle events with neuronal death in Alzheimer's disease. In this process, as discussed above, Aβ cause cell cycle reentry of adult neurons, leading to cell cycle associated apoptosis.

The cell cycle is regulated also by extracellular signaling from growth factors to the focal adhesion (FA) proteins. FA proteins are assembled into intracellular complexes regulating integrin-mediated communication between the extracellular matrix and the actin cytoskeleton (Caltagarone et al. 2007). Imoprtantly, fibrilar Aβ binds to integrins and mediate signal transduction from extracellular sites of Aβ deposition into the cell cycle by activation of the FA signaling pathways. FA-mediated control of the cell cycle involves such downstream signaling molecules as mitogen activated protein kinases (MAPK), as well as PI3, and GSK-3 kinases, which in turn control transcription and an interplay between cell cycle progression and neuronal survival (Caltagarone et al. 2007). The involvement of Aβ extracellular deposits in the signaling network points to the central role of Aβ and SP in the cell cycle related events during neurodegeneration in AD.

Aβ is also known to increase oxidative stress in the cell membrane and in membranes of intracellular compartments, including mitochondria (Wojda et al. 2008). Consistently, numerous data show a link between oxidative stress and mitochondria dysfunction in AD. The relationship between Aβ and mitochondrial oxidative stress is reciprocal in AD: the mitochondrial cascade hypothesis was proposed showing how the mitochondrial dysfunction in the late-onset, sporadic AD could be combined with the amyloid cascade (Swerdlow and Khan 2004). According to this hypothesis, mitochondrial dysfunction connected with elevated reactive oxygen species (ROS) production causes damage of cellular molecules and drives formation of SP and NTF. In summary, Aβ and oxidative stress represent a link between pathophysiological hallmarks of AD with DNA damage and cell cycle associated death of AD neurons.

TAU AND CELL CYCLE ASSOCIATED NEURONAL DEATH

Cell cycle activation associated with cell death was observed as an effect of phoshorylated tau protein, suggesting that phosphorylated tau is a potential insult triggering cell cycle associated apoptosis in tauopaties including AD (Andorfer et al. 2005). Overexpression of human tau in the mouse brain resulted in cell cycle reactivation, and lead to neuronal death (Delobel et al. 2006). Important data came from studies in *Drosophila* models of wild-type and mutant tau, which recapitulate tau-induced changes in synaptic plasticity and

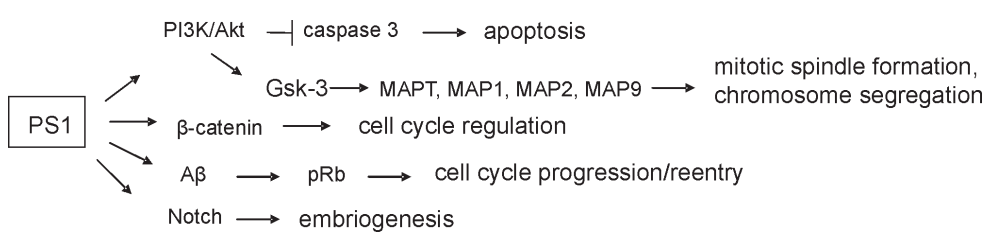

Fig. 2. Main Presenilin1 (PS1)-signaling pathways affecting embriogenesis and the cell cycle. Mutations in PS1 impair these processes resulting in aberrant cell cycle, aneuploidy and apoptosis.

neurotransmission. In these models phosphorylated tau activated target of rapamycic (TOR) kinase pathway, which in turn induced cell cycle activation followed immediately by apoptosis (Chee et al. 2005). Importantly, neurodegeneration induced by the TOR kinase in *Drosophila* was partially blocked by cell cycle inhibititors. The conclusion was that the TOR kinase pathway drives tau-induced neurodegeneration. Moreover, upregulation of the TOR kinase pathway has been found in association with cell cycle activation and with hiperphosphorylation of tau in AD brains (An et al. 2003, Arendt 2003, Li et al. 2005). Importantly, alterations of the TOR kinase signaling were reported not only in neurons, but also in lymphocytes from AD patients (Nagy et al. 2002). It seems that activation of the cell cycle and cell cycle associated apoptosis *via* the TOR kinase pathway by tau phosphorylation is a common mechanism in tauopathies. In contrast, TOR kinase activation was not found in *Drosophila* models of Parkinson's and Huntington's disease (Khurana et al. 2006). However, activation of cell cycle machinery was detected not only in postmortem vulnerable human brain regions in AD and other tauopathies, but also in transgenic mouse models of ataxia telangiectasia and of Parkinson's disease (Yang and Herrup 2007). Cell cycle activation in neurons was also reported in hypoxia-ischemia, stroke and ataxias (Kuan et al. 2004, Rashidian et al. 2007). Based on observed TOR pathway, active only in models of tauopathies, Khurana and coauthors (2006) suggest that mechanisms of neurodegeneration linked to cell cycle in different pathologies are distinct. Nevertheless, it remains uncertain whether cell cycle activation and associated cell death involve any universal pathways in many neurodegenerative processes and whether there are mechanisms specific only to AD.

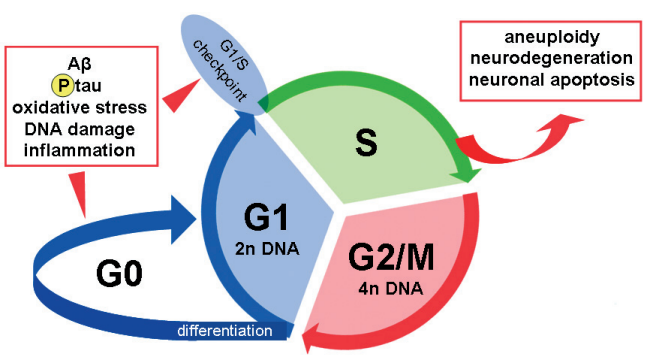

Fig. 3. Causes and consequences of cell cycle reentry in mature, differentiated neurons as an important pathogenic component in Alzheimer's disease. Mature differentiated neurons enter G_0 stage of the cell cycle and become resistant against mitogenic stimuli. However, prolonged, repetitive hits of proliferating signals (Aβ, phosphorylated tau, oxidative stress, DNA damage and inflammation) drive differentiated neurons into the cell cycle. Failure in G_1/S checkpoint allows DNA synthesis but the cycle does not progress beyond the S phase. It results in aneuploidy, neurodegeneration and cell death.

OTHER PATHWAYS INVOLVED IN CELL CYCLE ASSOCIATED DEATH OF NEURONS

There are other pathways in addition to TOR signaling that were implicated in mediation of cell cycle reentry in postmitotic neurons. One of them seems to be linked with ubiquitin-proteasome degradation pathway required to maintain postmitotic neuronal status, because downregulation of certain components of the pathway results in loss of neurons in primary cultures (Staropoli and Abeliovich 2005). Moreover, one of hypothesis on mechanism underlying cell cycle activation and cell death in neurons is "Dr. Jekyll and Mr. Hyde" concept based on demonstration of association of the origin recognition complex (ORC) with NFT pathology in AD (Arendt 2003). In proliferating cells, ORC control DNA replication as a point of convergence of multiple signaling pathways responsible for cell cycle progression and for apoptotic programs. In mammalian brain the ORC have been implicated in the regulation of synaptic plasticity and cognition and found to be abnormally distributed in AD neurons (Arendt and Bruckner 2007). It was proposed that ORC in AD compromise their physiological role in plasticity and get back to their primarily functions to control proliferation and de-repression of apoptotic programs. This concept provide a molecular link between loss of synaptic plasticity, DNA replication and cell death observed in AD but the underlying mechanisms are far from being fully elucidated.

Another protein at the cross-talk between Aβ, tau, and the cell cycle is PIN1, the peptidyl-prolyl cis/trans isomerase. PIN1 catalyzes isomerization of proteins phosphorylated at serine or threonine residues followed by proline (pSer/Thr-Pro motif). The isomerization of this motif represents an important regulatory mechanism of PIN1 substrates by modulating their phosphorylation status, catalytic activity, protein-pro-

tein interactions and stability (Suizu et al. 2006). PIN1 is involved in many cellular processes including proliferation and differentiation. Its overexpression induces centrosome duplication, chromosome instability, resulting in aneuploidy and oncogenesis (Suizu et al. 2006). Also inhibition of PIN1 influence cell cycle, suppressing centrosome duplication during S phase. Recent data point a role of PIN1 in protection against neurodegeneration, as PIN1 prevents phosphorylation of tau and processing of APP to Aβ (Balastik et al. 2007). The significant role of PIN1 in AD was demonstrated in the knock out Pin1 mouse model, where deletion of *Pin1* caused both tau and Aβ pathological changes in age-dependent manner (Suizu et al. 2006). In agreement with this, in the human AD brain *PIN1* is downregulated or inhibited by oxidation. The exact molecular connection between PIN1 depletion in AD and cell cycle associated cell death remains to be established.

Presenilins and their interactions with protein ligands that control cell cycle, such as β-catenin and GSK-3, were discussed earlier in this review. The molecular links between PS1 and PS2 in incomplete DNA replication and chromosome missegregation, and neuronal apoptosis are still under investigations.

While cell cycle reentry and associated apoptosis in postmitotic neurons seems to be a central process underlying neurodegeneration in AD, other pathways leading to apoptosis and cell death in AD were also described and contribute to massive loss of neurons in this pathology.

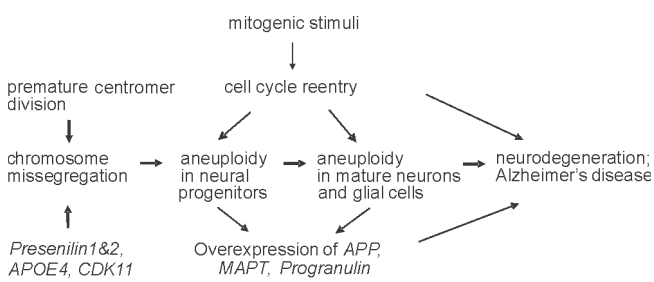

Fig. 4. Main pathways and factors causing increase in aneuploidy and cell cycle reentry followed by neurodegeneration in AD. An interplay between AD pathological elements such as aberrant cell cycle and aneuploidy in neural progenitors and in mature neurons as well as changes of presenilins, APP, MAPT and associated proteins result in neurodegeneration in AD. Detailed explanations in the text.

CONCLUSIONS

Defects of chromosome segregation or whole genome integrity could be an important player in Alzheimer's pathology. Schematic summary of possible levels of increase in aneuploidy leading to AD is shown on Fig. 2. Increased aneuploidy found in the brains and other tissues of AD patients could be a result of chromosomal missegregation, influenced by various environmental factors or age-related. Alternatively, mosaicism could be an effect of genetic predisposition to aneuploidy, which could lead to mosaicism both on meiotic level (germ cells) and at mitotic level. It is widely recognized that somatic mosaicism is an important contributor to genetic and phenotypic variation. Chromosomal mosaicism can result in substantial phenotypic changes, and in case of developing brain (either fetal or post-natal) can lead to abnormal physiology.

In particular, mutations in the presenilin genes that cause Alzheimer's disease could also cause chromosome instability. Mitotic missegregation could result in aneuploidy of neuronal progenitors, e.g. in the hippocampal area involved in neurogenesis. Mitotic missegregation in brain cells could lead to AD pathology by inducing inflammation, apoptosis, and amyloidogenic APP proteolysis, after decades of slow increase of aneuploidy level. A systematic screening of AD patients' brains using sensitive methods aimed at detection of chromosome loss and/or gain (like array comparative genomic hybridization, aCGH), as well as classical kariotyping are needed to establish the exact role of aneuploidy in the Alzheimer's disease pathology.

It seems also plausible that aneuploid cells could result from cell cycle re-entry, when neurons start or underwent DNA replication, and then stop. Such abortive induction of division induces commitment of cells to apoptosis, but aneuploid stem cells and neurons could often live and display an aberrant transcriptome profile. Hypothesis on the role of cell-cycle molecules deregulation unify all AD pathological elements, including AD causative factors (presenilin mutations, oxidative stress, chromosomal imbalance), proteins involved in AD (Aβ, MAPT), as well as AD histopathology.

Importantly, DNA content in neurons is increased in brain regions affected by AD pathology already early in progression of the disease. In contrast, neurons from

the affected regions in the later stages of AD, show nearly normal DNA content. These observations suggest that increased DNA level and cell cycle molecules in the brain could serve as markers for an early diagnosis of neurodegeneration in AD.

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REFERENCES

Alexson TO, Hitoshi S, Coles BL, Bernstein A, van der Kooy D (2006) Notch signaling is required to maintain all neural stem cell populations – irrespective of spatial or temporal niche. Dev Neurosci 28: 34–48.

Alliegro MC, Alliegro MA (2008) Centrosomal RNA correlates with intron-poor nuclear genes in Spisula oocytes. Proc Natl Acad Sci U S A 105: 6993–6997.

An WL, Cowburn RF, Li L, Braak H, Alafuzoff I, Iqbal K, Iqbal IG, Winblad B, Pei JJ (2003) Up-regulation of phosphorylated/activated p70 S6 kinase and its relationship to neurofibrillary pathology in Alzheimer's disease. Am J Pathol 163: 591–607.

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.

Appert-Collin A, Hugel B, Levy R, Niederhoffer N, Coupin G, Lombard Y, André P, Poindron P, Gies JP (2006) Cyclin dependent kinase inhibitors prevent apoptosis of postmitotic mouse motoneurons. Life Sci 79: 484–490.

Arendt, T (1993) Neuronal dedifferentiation and degeneration in Alzheimer´s disease. Biol.Chem. Hoppe-Seyler 374: 911–912.

Arendt T, Brückner MK, Gertz HJ, Marcova L (1998) Cortical distribution of neurofibrillary tangles in Alzheimer's disease matches the pattern of neurons that retain their capacity of plastic remodelling in the adult brain. Neuroscience 83: 991–1002.

Arendt T (2003) Synaptic plasticity and cell cycle activation in neurons are alternative effector pathways: the "Dr. Jekyll and Mr. Hyde concept" of Alzheimer's disease or the yin and yang of neuroplasticity. Prog Neurobiol 71: 83–248.

Arendt T, Brückner MK (2007) Linking cell-cycle dysfunction in Alzheimer's disease to a failure of synaptic plasticity. Biochim Biophys Acta 1772: 413–421.

Avramopoulos D, Mikkelsen M, Vassilopoulos D, Grigoriadou M, Petersen MB (1996) Apolipoprotein E allele distribution in parents with Down's syndrome children. Lancet 347: 862–865.

Bajic VP, Spremo-Potparevic B, Zivkovic L, Djelic N, Smith MA (2008) Is the time dimension of the cell cycle re-entry in AD regulated by centromere cohesion dynamics? Biosci Hypoth 1: 156–161.

Baki L, Neve RL, Shao Z, Shioi J, Georgakopoulos A, Robakis NK (2008) Wild-type but not FAD mutant presenilin-1 prevents neuronal degeneration by promoting phosphatidylinositol 3-kinase neuroprotective signaling. J Neurosci 28: 483–490.

Baki L, Shioi J, Wen P, Shao Z, Schwarzman A, Gama-Sosa M, Neve R, Robakis NK (2004) PS1 activates PI3K thus inhibiting GSK-3 activity and tau overphosphorylation: effects of FAD mutations. EMBO J 23: 2586–2596.

Balastik M, Lim J, Pastorino L, Lu KP (2007) Pin1 in Alzheimer's disease: Multiple substrates, one regulatory mechanism? Biochim Biophys Acta 1772: 422–442.

Baas PW (1999) Microtubules and neuronal polarity: lessons from mitosis. Neuron 22: 23–31.

Battaglia F, Quartarone A, Rizzo V, Ghilardi MF, Di Rocco A, Tortorella G, Girlanda P (2008) Early impairment of synaptic plasticity in patients with Down's syndrome. Neurobiol Aging 29: 1272–1275.

Bertram L, Tanzi RE (2008) Thirty years of Alzheimer's disease genetics: the implications of systematic meta-analyses. Nat Rev Neurosci 9: 768–778.

Blom ES, Viswanathan J, Kilander L, Helisalmi S, Soininen H, Lannfelt L, Ingelsson M, Glaser A, Hiltunen M (2008) Low prevalence of APP duplications in Swedish and Finnish patients with early-onset Alzheimer's disease. Eur J Hum Genet 16: 171–175.

Boeras DI, Granic A, Padmanabhan J, Crespo NC, Rojiani AM, Potter H (2008) Alzheimer's presenilin 1 causes chromosome missegregation and aneuploidy. Neurobiol Aging 29: 319–328.

Buckton KE, Whalley LJ, Lee M (1983) Chromosome changes in Alzheimer's presenile dementia. J Med Genet 20: 46–51.

Busciglio J, Yankner BA (1997) Apoptosis and increased generation of reactive oxygen species in Down's syndrome neurons in vitro. Nature 378: 776–779.

Caltagarone J, Jing Z, Bowser R (2007) Focal adhesions regulate Aβ signaling and cell death in Alzheimer's disease. Biochim Biophys Acta 1772: 438–445.

Cenini G, Sultana R, Memo M, Butterfield DA (2008) Elevated levels of pro-apoptotic p53 and its oxidative modification by the lipid peroxidation product, HNE, in brain from subjects with amnestic mild cognitive impairment and Alzheimer's disease. J Cell Mol Med 12: 987–994.

Checler F, Sunyach C, Pardossi-Piquard R, Sévalle J, Vincent B, Kawarai T, Girardot N, St George-Hyslop P, da Costa CA (2007) The gamma/epsilon-secretase-derived APP intracellular domain fragments regulate p53. Curr Alzheimer Res 4: 423–426.

Chee FC, Mudher A, Cuttle MF, Newman TA, MacKay D, Lovestone S, Shepherd D (2005) Over-expression of tau results in defective synaptic transmission in Drosophila neuromuscular junctions. Neurobiol Dis 20: 918–928.

Chen P, Zindy F, Abdala C, Liu F, Li X, Roussel MF, Segil N (2003) Progressive hearing loss in mice lacking the cyclin-dependent kinase inhibitor Ink4d. Nat Cell Biol 5: 422–426.

Chevallier NL, Soriano S, Kang DE Masliah E, Hu G, Koo EH (2005) Perturbed neurogenesis in the adult hippocampus associated with presenilin 1 A246E mutation. Am J Pathol 167: 151–159.

Chiang PK, Lam MA, Luo Y (2008) The many faces of amyloid beta in Alzheimer's disease. Curr Mol Med 8: 580–584.

Contestabile A, Fila T, Ceccarelli C, Bonasoni P, Bonapace L, Santini D, Bartesaghi R, Ciani E (2007) Cell cycle alteration and decreased cell proliferation in the hippocampal dentate gyrus and in the neocortical germinal matrix of fetuses with Down syndrome and in Ts65Dn mice. Hippocampus 17: 665–678.

Copani A, Caraci F, Hoozemans JM, Calafiore M, Sortino A (2007) The nature of the cell cycle in neurons: Focus on a "non-canonical" pathway of DNA replication causally related to death. Biochim Biophys Acta 1772: 409–412.

Cruts M, Van Broeckhoven C (1998) Molecular genetics of Alzheimer's disease. Ann Med 30: 60–65.

Dickey CA, Loring JF, Montgomery J, Gordon MN, Eastman PS, Morgan D (2003) Selectively reduced expression of synaptic plasticity-related genes in amyloid precursor protein + presenilin-1 transgenic mice. J Neurosci 23: 5219–5226.

Dehmelt L, Halpain S (2005) The MAP2/Tau family of microtubule-associated pr teins. Genome Biol 6: 204.

Delobel P, Lavenir I, Ghetti B, Holzer M, Goedert M (2006) Cell-cycle markers in a transgenic mouse model of human tauopathy: increased levels of cyclin-dependent kinase inhibitors p21Cip1 and p27Kip1. Am J Pathol 168: 878–887.

Dranovsky A, Oxberry W, Lyubsky S, Goldgaber D (1996) APP is associated with mitotic centrosomes and a distinct cytoplasmic network which colocalizes with depolymerized tubulin. Neurobiol Aging 17 (Suppl. 1): S196.

Ezquerra M, Ballesta F, Queralt R, Aledo R, Gómez D, Guitart M, Egozcue J, Ascaso C, Oliva R (1998) Apolipoprotein E epsilon 4 alleles and meiotic origin of non-disjunction in Down syndrome children and in their corresponding fathers and mothers. Neurosci Lett 248: 1–4.

Friedberg EC, Walker GC, Siede W, Wood RD, Schultz RA, Ellenberger T (2006) DNA Repair and Mutagenesis. Part 3. (2nd ed.). ASM Press, Herndon, VA.

Galli C, Piccini A, Ciotti MT, Castellani L, Calissano P, Zaccheo D, Tabaton M (1998) Increased amyloidogenic secretion in cerebellar granule cells undergoing apoptosis. Proc Natl Acad Sci U S A 95: 1247–1252.

Gatz M, Reynolds CA, Fratiglioni L, Johansson B, Mortimer JA, Berg S, Fiske A, Pedersen NL (2006) Role of genes and environments for explaining Alzheimer disease. Arch Gen Psychiatry 63: 168–174.

Geller LN, Potter H (1999) Chromosome mis-segregation and trisomy 21 mosaicism in Alzheimer's disease. Neurobiol Dis 6: 167–179.

Gent van DC, Hoeijmakes JH, Kanaar R (2001) Chromosomal stability and the DNA double-stranded break connection. Nat Rev Genet 2: 196–206.

Giménez-Llort L, Blázquez G, Cañete T, Johansson B, Oddo S, Tobeña A, LaFerla FM, Fernández-Teruel A (2007) Modeling behavioral and neuronal symptoms of Alzheimer's disease in mice: a role for intraneuronal amyloid. Neurosci Biobehav Rev 31: 125–147.

Goodwin B, Padmanabhan J, Granic A, Owens C, CrespoN, Potter H (2008) Inhibition of gamma-secretase activity induces cell cycle defects and chromosome missegregation. Alzheimers Dement 4 (Suppl. 1): T614.

Harbour JW, Dean DC (2000) Rb function in cell-cycle regulation and apoptosis, Nat Cell Biol 2: E65–E67.

Hardy OJ, Goate A, Owen M, Rossor M (1989) Presenile dementia associated with mosaic trisomy 21 in a patient with a Down syndrome child. Lancet 8665: 743.

Heintz N (1993) Cell death and the cell cycle: a relationship between transformation and neurodegeneration? Trends Biochem Sci 18: 157–159.

Herrup K, Arendt T (2002) Re-expression of cell cycle proteins induce neuronal cell death during Alzheimer's disease. J Alzheimers Dis 4: 243–247.

Herrup K, Neve R, Ackerman SL, Copani A (2004) Divide and die: cell cycle events as triggers of nerve cell death. J Neurosci 24: 9232–9239.

Herrup K, Cohen M, Chen J, Yang Y, Lerner A (2008) Cell cycle events implicate cerebellar dentate nucleus neurons as targets of Alzheimer pathology. Alzheimers Dement 4 (Suppl. 1): T614.

Heston LL, Mastri AR, Anderson VE, White J (1981) Dementia of the Alzheimer type. Arch Gen Psychiatr 38: 1084–1090.

Heyman A, Wilkinson W, Hurwitz B, Schmechel D, Sigmon AH, Weinberg T, Helms MJ, Swift M (1983) Alzheimer's disease genetic aspects and associated clinical disorders. Ann Neurol 14: 507–515.

Higuchi Y (2003) Chromosomal DNA fragmentation in apoptosis and necrosis induced by oxidative stress. Biochem Pharmacol 66: 1527–1535.

Honda T, Nihonmatsu N, Yasutake K, Ohtake A, Sato K, Tanaka S, Murayama O, Murayama M, Takashima A (2000) Familial Alzheimer's disease-associated mutations block translocation of full-length presenilin 1 to the nuclear envelope. Neurosci Res 37: 101–111.

Illenberger S, Zheng-Fischhöfer Q, Preuss U, Stamer K, Baumann K, Trinczek B, Biernat J, Godemann R, Mandelkow EM, Mandelkow E (1998) The endogenous and cell cycle-dependent phosphorylation of tau protein in living cells: implications for Alzheimer's disease. Mol Biol Cell 9: 1495–1512.

Iourov IY, Liehr T, Vorsanova SG, Kolotii AD, Yurov YB (2006) Visualization of interphase chromosomes in postmitotic cells of the human brain by multicolour banding (MCB). Chromosome Res 14: 223–229.

Iourov IY, Liehr T, Vorsanova SG, Yurov YB (2007) Interphase chromosome-specific multicolor banding (ICS-MCB): a new tool for analysis of interphase chromosomes in their integrity. Biomol Eng 24: 415–417.

Iourov IY, Vorsanov SG, Liehr T, Kolotii AD, Soloviev IV, Vostrikov VM, Uranova NA, Yurov YB (2008) Association of genome instability and neurodegeneration in the cerebral cortex and hippocampus in Alzheimer's disease brain: Evidences for a new pathogenetic mechanism of the disease. Int J Psychophysiol 69: 288.

Janicki SM, Monteiro MJ (1999) Presenilin overexpression arrests cells in the G1 phase of the cell cycle: arrest potentiated by the Alzheimer's disease PS2 (N141I) Mutant. Am J Pathol 155: 135–144.

Jellinger KA, Bancher C (1998) Neuropathology of Alzheimer's disease: A critical update J Neural Transm Suppl 54: 77–95.

Jeong SJ, Kim HS, Chang KA, Geum DH, Park CH, Seo JH, Rah JC, Lee JH, Choi SH, Lee SG, Kim K, Suh YH (2000) Subcellular localization of presenilins during mouse preimplantation development. FASEB J 14: 2171–2176.

Jiang Q, Lee CY, Mandrekar S, Wilkinson B, Cramer P, Zelcer N, Mann K, Lamb B, Willson TM, Collins JL, Richardson JC, Smith JD, Comery TA, Riddell D, Holtzman DM, Tontonoz P, Landreth GE (2008) ApoE promotes the proteolytic degradation of Abeta. Neuron 58: 681–693.

Jin K, Galvan V, Xie L, Mao XO, Gorostiza OF, Bredesen DE, Greenberg DA (2004) Enhanced neurogenesis in Alzheimer's disease transgenic (PDGF-APPw,Ind) mice. Proc Natl Acad Sci U S A 101: 13363–13367.

Jin K, Peel AL, Mao XO, Xie L, Cottrell BA, Henshall DC, Greenberg DA (2004) Increased hippocampal neurogenesis in Alzheimer's disease. Proc Natl Acad Sci U S A 101: 343–347.

Johnsingh AA, Johnston JM, Merz G, Xu J, Kotula L, Jacobsen JS, Tezapsidis N (2000). Altered binding of mutated presenilin with cytoskeleton-interacting proteins. FEBS Lett 465 53–58.

Kuhn HG, Cooper-Kuhn CM, Boekhoorn K, Lucassen PJ (2007) Changes in neurogenesis in dementia and Alzheimer mouse models: are they functionally relevant? Eur Arch Psychiatry Clin Neurosci 257: 281–289.

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.

Kimura N, Nakamura SI, Honda T, Takashima A, Nakayama H, Ono F, Sakakibara I, Doi K, Kawamura S, Yoshikawa Y (2001) Age-related changes in the localization of presenilin-1 in cynomolgus monkey brain. Brain Res 922: 30–41.

Kingsbury MA, Friedman B, McConnell MJ, Rehen SK, Yang AH, Kaushal D, Chun J (2005) Aneuploid neurons are functionally active and integrated into brain circuitry. Proc Natl Acad Sci U S A 102: 6143–6147.

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.

Knobloch M, Konietzko U, Krebs DC, Nitsch RM (2007) Intracellular Abeta and cognitive deficits precede beta-amyloid deposition in transgenic arcAbeta mice. Neurobiol Aging 28: 1297–1306.

Konishi Y, Bonni A (2003) The E2F-Cdc2 cell-cycle pathway specifically mediates activity deprivation-induced apoptosis of postmitotic neurons. J Neurosci 23: 1649–1658.

Konietzko U, Goodger ZV, Meyer M, Kohli BM, Bosset J, Lahiri DK, Nitsch RM (2008) Co-localization of the amy-

loid precursor protein and Notch intracellular domains in nuclear transcription factories. Neurobiol Aging (Epub ahead of print): doi:10.1016/j.neurobiolaging.2008.03.001

Korczyn AD (2008) The amyloid cascade hypothesis. Alzheimers Dement 4: 176–178.

Kovaleva NV (2007) Parental mosaicism for trisomy 21: problems with its detection and an approach to determining its population rate. Genet Test 11: 341–344.

Kruman II, Kumaravel TS, Lohani A, Pedersen WA, Cutler RG, Kruman Y, Haughey N, Lee J, Evans M, Mattson MP (2002) Folic acid deficiency and homocysteine impair DNA repair in hippocampal neurons and sensitize them to amyloid toxicity in experimental models of Alzheimer's disease. J Neurosci 22: 1752–1762.

Kruman II, Wersto RP, Cardozo-Pelaez F, Smilenov L, Chan SL, Chrest FJ, Emokpae R Jr, Gorospe M, Mattson MP (2004) Cell cycle activation linked to neuronal cell death initiated by DNA damage. Neuron 41: 549–561.

Kuan CY, Schloemer AJ, Lu A, Burns KA, Weng WL, Williams MT, Strauss KI, Vorhees CV, Flavell RA, Davis RJ, Sharp FR, Rakic P (2004) Hypoxia-ischemia induces DNA synthesis without cell proliferation in dying neurons in adult rodent brain. J Neurosci 24: 10763–10772.

Lanni C, Racchi M, Mazzini G, Ranzenigo A, Polotti R, Sinforiani E, Olivari L, Barcikowska M, Styczynska M, Kuznicki J, Szybinska A, Govoni S, Memo M, Uberti D (2008) Conformationally altered p53: a novel Alzheimer's disease marker? Mol Psychiatry 13: 641–647.

Lao JL, Beyer K, Fernández-Novoa L, Miguel-Hidalgo JJ, Vecino B, Alvarez XA, Cacabelos R (1996) Cytogenetic signs of genomic instability in Alzheimer's disease. Neurobiol Aging 17: S62–63.

Larner AJ (2008) Mutation negative "early-onset familial Alzheimer disease": consider screening for tau gene mutations. Alzheimer Dis Assoc Disord 22: 194–195.

Lee EY, Chang CY, Hu N, Wang YC, Lai CC, Herrup K, Lee WH, Bradley A (1992) Mice deficient for Rb are nonviable and show defects in neurogenesis and haematopoiesis. Nature 359: 288–294.

Lee HG, Zhu X, Castellani RJ, Nunomura A, Perry G, Smith MA (2007) Amyloid-beta in Alzheimer disease: the null versus the alternate hypotheses. J Pharmacol Exp Ther 321: 823–829.

Lee H, Zhu X, Richardson S, Perry G, Smith M (2008) Failure in the control of cell cycle causes neurodegeneration. Alzheimers Dement 4 (Suppl. 1): T614-T615.

LeBlank A (1995) Increased production of 4KDa amyloid beta peptide in serum-deprived human primary neuron cultures: possible involvement of apoptosis. J Neurosci 15: 7837–7846.

Li B, Yamamori H, Tatebayashi Y, Shafit-Zagardo B, Tanimukai H, Chen S, Iqbal K, Grundke-Iqbal I (2008) Failure of neuronal maturation in Alzheimer disease dentate gyrus. J Neuropathol Exp Neurol 67: 78–84.

Li J, Xu M, Zhou H, Ma J, Potter H (1997) Alzheimer presenilins in the nuclear membrane, interphase kinetochores, and centrosomes suggest a role in chromosome segregation. Cell 90: 917–927.

Li X, Alafuzoff I, Soininen H, Winblad B, Pei JJ (2005) Levels of mTOR and its downstream targets 4E-BP1, eEF2 and eEF2 kinase in relationships with tau in Alzheimer's disease brain. FEBS J 272: 4211–4220.

Liu L, Li Y, Van Eldik LJ, Griffin WS, Barger SW (2005) S100B-induced microglial and neuronal IL-1 expression is mediated by cell type-specific transcription factors. J Neurochem 92: 546–553.

Love S, Barber R, Wilcock GK (1999) Increased polyADP-ribosylation of nuclear proteins in Alzheimer's disease. Brain 122: 247–253.

Lovell MA, Xie C, Markesbery WR (2000) Decreased base excision repair and increased helicase activity in Alzheimer's disease brain. Brain Res 855: 116–123.

Lucarelli P, Piciullo A, Palmarino M, Verdecchia M, Saccucci P, Arpino C, Curatolo P (2004) Association between presenilin 1 – 48c/t polymorphism and Down's syndrome. Neurosci Lett 367: 88–91.

Ma D, Zhou P, Harbour JW (2003) Distinct mechanisms for regulating the tumor suppressors and antiapoptotic functions of Rb. J Biol Chem 278: 19358–19366.

Matrone C, Ciotti MT, Mercanti D, Marolda R, Calissano P (2008) NGF and BDNF signaling control amyloidogenic route and Abeta production in hippocampal neurons. Proc Natl Acad Sci U S A 105: 13139–13144.

McDonald DR, Bamberger ME, Combs CK, Landreth GE (2008) Beta-amyloid fibrils activate parallel mitogen-activated protein kinase pathways in microglia and THP1 monocytes. J Neurosci 18: 4451–60.

McPhie DL, Coopersmith R, Hines-Peralta A, Chen Y, Ivins KJ, Manly SP, Kozlowski MR, Neve KA, Neve RL (2003) DNA synthesis and neuronal apoptosis caused by familial Alzheimer disease mutants of the amyloid precursor protein are mediated by the p21 activated kinase PAK3. J Neurosci 23: 6914–6927.

McShea A, Wahl AF, Smith MA (1999) Re-entry into the cell cycle: a mechanism for neurodegeneration in Alzheimer disease. Med Hypotheses 52: 525–527.

McShea A, Lee H, 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.

Mehes K, Kosztolanyi G (2004) Clinical manifestation of genetic instability oerlap one another. Pathol Oncol Res 10: 12–16.

Mensah A, Mulligan C, Linehan J, Ruf S, O'Doherty A, Grygalewicz B, Shipley J, Groet J, Tybulewicz V, Fisher E, Brandner S, Nizetic D (2007) An additional human chromosome 21 causes suppression of neural fate of pluripotent mouse embryonic stem cells in a teratoma model. BMC Dev Biol 29: 131.

Migliore L, Botto N, Scarpato R, Petrozzi L, Cipriani G, Bonuccelli U (1999) Preferential occurrence of chromosome 21 malsegregation in peripheral blood lymphocytes of Alzheimer disease patients. Cytogenet Cell Genet 87: 41–46.

Migliore L, Testa A, Scarpato R, Pavese N, Petrozzi L, Bonuccelli U (1997) Spontaneous and induced aneuploidy in peripheral blood lymphocytes of patients with Alzheimer's disease. Hum Genet 101: 299–305.

Migliore L, Fontana I, Trippi F, Colognato R, Coppedè F, Tognoni G, Nucciarone B, Siciliano G (2005) Oxidative DNA damage in peripheral leukocytes of mild cognitive impairment and AD patients. Neurobiol Aging 26: 567–573.

Migliore L, Boni G, Bernardini R, Trippi F, Colognato R, Fontana I, Coppede F, Sbrana I (2006) Susceptibility to chromosome malsegregation in lymphocytes of women who had a Down syndrome child in a young age. Neurobiol Aging 27: 710–716.

Miyata M, Smith JD (1996) Apolipoprotein E allele-specific antioxidant activity and effects on cytotoxicity by oxidative insults and beta-amyloid peptides. Nat Genet 14: 55–61.

Moehlmann T, Winkler E, Xia X, Edbauer D, Murrell J, Capell A, Kaether C, Zheng H, Ghetti B, Haass C, Steiner H (2002) Presenilin-1 mutations of leucine 166 equally affect the generation of the Notch and APP intracellular domains independent of their effect on Abeta 42 production. Proc Natl Acad Sci U S A 99: 8025–8030.

Moorhead PS, Heyman A (1983) Chromosome studies of patients with Alzheimer's disease. Am J Med Genet 14: 545–556.

Mosch B, Morawski M, Mittag A, Lenz D, Tarnok A, Arendt A (2007) Aneuploidy and DNA replication in the normal human brain and Alzheimer's disease. J Neurosci 27: 6859–6867.

Mrak RE, Griffin WS (2004) Trisomy 21 and the brain. J Neuropathol Exp Neurol 63: 679–685.

Mrak RE, Griffin WS (2005) Glia and their cytokines in progression of neurodegeneration. Neurobiol Aging 26: 349–354.

Mullaart E, Boerrigter ME, Ravid R, Swaab DF, Vijg J (1990) Increased levels of DNA breakes in cerebral cortex of Alzheimer's patients. Neurobiol Aging 11: 169–173.

Nagarsheth MH, Viehman A, Lippa SM, Lippa CF (2006) Notch-1 immunoexpression is increased in Alzheimer's and Pick's disease. J Neurol Sci 244: 111–116.

Nagy Z, Esiri MM, Smith AD (1998) The cell division cycle and the pathophysiology of Alzheimer's disease Neurosci 87: 731–739.

Nagy Z (2000) Cell cycle regulatory failure in neurons: causes and consequences. Neurobiol Aging 21: 761–769.

Nagy Z, Combrinck M, Budge M, McShane R (2002) Cell cycle kinesis in lymphocytes in the diagnosis of Alzheimer's disease. Neurosci Lett 317: 81–84.

Nagy Z (2007) The dysregulation of the cell cycle and the diagnosis of Alzheimer's disease. Biochim Biophys Acta 1772: 402–408.

Nordenson I, Adolfsson R, Beckman G, Bucht G, Winblad B (1980) Chromosomal abnormality in dementia of Alzheimer type. Lancet 8166: 481–482.

Nouspikel T, Hanawalt PC (2003) When parsimony backfires: neglecting DNA repair may doom neurons in Alzheimer's disease. Bioessays 25: 168–173.

Nussbaum RL, Ellis CE (2003) Alzheimer's disease and Parkinson's disease. N Engl J Med 348: 1356–1364.

O'Doherty A, Ruf S, Mulligan C, Hildreth V, Errington ML, Cooke S, Sesay A, Modino S, Vanes L, Hernandez D, Linehan JM, Sharpe PT, Brandner S, Bliss TV, Henderson DJ, Nizetic D, Tybulewicz VL, Fisher EM (2005) An aneuploid mouse strain carrying human chromosome 21 with Down syndrome phenotypes. Science 309: 2033–2037.

Ohyagi Y, Asahara H, Chui DH, Tsuruta Y, Sakae N, Miyoshi K, Yamada T, Kikuchi H, Taniwaki T, Murai H, Ikezoe K, Furuya H, Kawarabayashi T, Shoji M, Checler F, Iwaki T, Makifuchi T, Takeda K, Kira J, Tabira T (2005) Intracellular Abeta42 activates p53 promoter: a pathway to neurodegeneration in Alzheimer's disease. FASEB J 19: 255–257.

Okochi M, Fukumori A, Jiang J, Itoh N, Kimura R, Steiner H, Haass C, Tagami S, Takeda M (2006) Secretion of the

Notch-1 Abeta-like peptide during Notch signaling. J Biol Chem 281: 7890–8.

Oyama F, Cairns NJ, Shimada H, Oyama R, Titani K, Ihara Y (1994) Down's syndrome: Up-regulation of beta-amyloid protein precursor and tau mRNAs and their defective coordination. J Neurochem 62: 1062–1066.

Park DS, Obeidat A, Giovanni A, Greene LA (2000) Cell cycle regulators in neuronal death evoked by excitotoxic stress: implications for neurodegeneration and its treatment, Neurobiol Aging 21: 771–781.

Pastor P, Goate AM (2004) Molecular genetics of Alzheimer's disease. Curr. Psychiatry Rep. 6: 125–133.

Patterson D, Costa A (2005) Down syndrome and genetics – a case of linked histories. Nat Rev Genet 6: 137–147.

Percy ME, Markovic VD, McLachlan DR, Berg JM, Hummel JT, Laing ME, Dearie TG, Andrews DF (1991) Family with 22-derived marker chromosome and late-onset dementia of the Alzheimer type: I. Application of a new model for estimation of the risk of disease associated with the marker. Am J Med Genet 39: 307–313.

Petersen MB, Karadima G, Samaritaki M, Avramopoulos D, Vassilopoulos D, Mikkelsen M (2000) Association between presenilin-1 polymorphism and maternal meiosis II errors in Down syndrome. Am J Med Genet 93: 366–372.

Petronis A (1999) Alzheimer's disease and Down syndrome: from meiosis to dementia. Exper Neurol 58: 401–413.

Pigino G, Pelsman A, Mori H, Busciglio J (2001) Presenilin-1 mutations reduce cytoskeletal association, deregulate neurite growth, and potentiate neuronal dystrophy and tau phosphorylation. J Neurosci 21: 834–842.

H. Potter (1991) Review and hypothesis: Alzheimer disease and Down syndrome. Chromosome 21 nondisjunction may underlie both disorders. Am J Hum Genet 48: 1192–1200.

Potter H (2005) Cell cycle and chromosome segregation defects in Alzheimer's disease. In: Cell-cycle mechanisms and neuronal death (Copani A, Nicoletti F, eds), pp 55–78. Georgetown, TX: Landes.

Potter H (2008) Down's syndrome and Alzheimer's disease: two sides of the same coin. Future Neurol 3: 29–37.

Potter H, Granic A, Boeras D, Crespo N, Padmanabhan J (2008) Alzheimer's mutant presenilin-1 and amyloid precursor protein genes cause chromosome missegregation and aneuploidy through the action of Abeta peptide. Alzheimer's and Dementia 4, Suppl 1, T346.

Potter H, Wefes IM, Nilsson LNG (2001) The inflammation induced pathological chaperones ACT and apoe4 are necessary catalysts of Alzheimer amyloid formation. Neurobiol Aging 22: 923–930.

Prasher VP, Farrer MJ, Kessling AM, Fisher EM, West RJ, Barber PC, Butler AC (1998) Molecular mapping of Alzheimer-type dementia in Down's syndrome. Ann Neurol 43: 380–383.

Raina AK, Zhu X, Smith MA (2004) Alzheimer's disease and the cell cycle. Acta Neurobiol Exp (Wars) 64: 107–112.

Rashidian J, Iyirhiaro GO, Park DS (2007) Cell cycle machinery and stroke. Biochim Biophys Acta 1772: 484–493.

Rauk A (2008) Why is the amyloid beta peptide of Alzheimer's disease neurotoxic? Dalton Trans 14: 1273–1282.

Reddy PH, McWeeney S, Park PB, Manczak M, Gutala RV, Partovi D, Jung Y, Yau V, Searles R, Mori M, Quinn J (2004) Gene expression profiles of transcripts in amyloid precurson protein transgenic mice: up-regulation of mitochondrial metabolism and apoptotic genes is an early cellular change in Alzheimer's disease. Hum Mol Genet 13: 1225–1240.

Rehen SK, Yung YC, McCreight MP, Kaushal D, Yang AH, Almeida BS, Kingsbury MA, Cabral KM, McConnell MJ, Anliker B, Fontanoz M, Chun J (2005) Constitutional aneuploidy in the normal human brain. J Neurosci 25: 2176–2180.

Richards BW (1974) Investigation of 142 mosaic mongols and mosaic parents of mongols: cytogenetic analysis and maternal age of birth. J Ment Defic Res 18: 199–204.

Rideout HJ, Wang Q, Park DS, Stefanis L (2003) Cyclin-dependent kinase activity is required for apoptotic death but not inclusion formation in cortical neurons after proteasomal inhibition. J Neurosci 23: 1237–1245.

Ringman JM, Rao PN, Lu PH, Cederbaum S (2008) Mosaicism for trisomy 21 in a patient with young-onset dementia: a case report and brief literature review. Arch Neurol 65: 412–415.

Rovelet-Lecrux A, Hannequin D, Raux G, Le Meur N, Laquerrière A, Vital A, Dumanchin C, Feuillette S, Brice A, Vercelletto M, Dubas F, Frebourg T, Campion D (2006) APP locus dupication causes autosomal dominant early-onset Alzheimer's disease with cerebral amyloid angiopathy. Nat Genet 38: 24–26.

Rowe IF, Ridler MAC, Gibberd FB (1989) Presenile dementia associated with mosaic trisomy 21 in a patient with a Down syndrome child. Lancet 8656: 229.

Sala SG, Muñoz U, Bartolomé F, Bermejo F, Martín-Requero A (2008) HMG-CoA reductase inhibitor simvastatin inhibits cell cycle progression at the G1/S checkpoint in immortalized lymphocytes from Alzheimer's

disease patients independently of cholesterol-lowering effects. J Pharmacol Exp Ther 324: 352–359.

Salehi A, Faizi M, Belichenko PV, Mobley WC (2007) Using mouse models to explore genotype-phenotype relationship in Down syndrome. Ment Retard Dev Disabil Res Rev 13: 207–214.

Schupf N, Kapell D, Lee JH, Ottman R, Mayeux R (1994) Increased risk of Alzheimer's disease in mothers of adults with Down's syndrome. The Lancet 344: 353–356.

Schupf N, Kapell D, Nightingale B, Lee JH, Mohlenhoff J, Bewley S, Ottman R, Mayeux R (2001) Specificity of the fivefold increase in AD in mothers of adults with Down syndrome. Neurology 57: 979–984.

Schindowski K, Belarbi K, Bretteville A, Ando K, Buée L (2008) Neurogenesis and cell cycle-reactivated neuronal death during pathogenic tau aggregation. Genes Brain Behav 7 (Suppl. 1): 92–100.

Słomnicki LP, Leśniak W (2008) A putative role of the Amyloid Precursor Protein Intracellular Domain (AICD) in transcription Acta Neurobiol Exp (Wars) 68: 219–228.

Spremo-Potparevic, Zivkivic L, Djelic N, Bajic V (2004) Analysis of premature centromere division (PCD) of the X chromosome in Alzheimer patients through the cell cycle. Exp Gerontol 39: 849–854.

Spremo-Potparević B, Zivković L, Djelić N, Plećas-Solarović B, Smith MA, Bajić V (2008) Premature centromere division of the X chromosome in neurons in Alzheimer's disease. J Neurochem 106: 2218–223.

Staessen C, Maes AM, Kirsch-Volders M, Susanne C (1983) Is there a predisposition for meiotic non-disjunction that may be detected by mitotic hyperploidy? Clinical Genetics 24: 184–190.

Stanton LR, Coetzee RH (2004) Down's syndrome and dementia. Adv Psych Treatment 10: 50–58.

Staropoli JF, Abeliovich A (2005) The ubiquitin-proteasome pathway is necessary for maintenance of the postmitotic status of neurons. J Mol Neurosci 27: 175–183.

Strittmatter WJ, Roses D (1995) Apolipoprotein E and Alzheimer disease. Proc Natl Acad Sci U S A 92: 4725–4727.

Suizu A, Ryo G, Wulf J, Lim J, Lu KP (2006) Pin1 regulates Centrosome Duplication, and its overexpression induces centrosome amplification, chromosome instability, and oncogenesis. Mol Cell Biol 26: 1463–1479.

Suram A, Hegde ML, Rao KS (2007) A new evidence for DNA nicking property of amyloid beta-peptide (1-42): relevance to Alzheimer's disease. Arch Biochem Biophys 463: 245–252

Suzuki T, Oishi M, Marshak DR, Czernik AJ, Nairn AC, Greengard P (1994) Cell cycle-dependent regulation of the phosphorylation and metabolism of the Alzheimer amyloid precursor protein. EMBO J 13: 1114–1122.

Swerdlow RH, Khan SM (2004) A "mitochondrial cascade hypothesis" for sporadic Alzheimer's disease. Med Hypotheses 63: 8–20.

Tagami S, Okochi M, Fukumori A, Jiang J, Yanagida K, Nakayama T, Morihara T, Tanaka T, Kudo T, Takeda M (2008) Processes of beta-amyloid and intracellular cytoplasmic domain generation by presenilin/gamma-secretase. Neurodegener Dis 5: 160–162.

Taupin P (2008) Alzheimer's disease, aneuploidy and neurogenesis. Med Sci Monit 14: LE6–6.

Teller JK, Russo C, DeBusk LM, Angelini G, Zaccheo D, Dagna-Bricarelli F, Scartezzini P, Bertolini S, Mann DM, Tabaton M, Gambetti P (1996) Presence of soluble amyloid β-peptide precedes amyloid plaque formation in Down's syndrome. Nature Medicine 2: 93–95.

Tezapsidis N, Merz PA, Merz G, Hong H (2003) Microtubular interactions of presenilin direct kinesis of Abeta peptide and its precursor. FASEB J 17: 1322–1324.

Thakur A, Siedlak SL, James SL, Bonda DJ, Rao A, Webber KM, Camins A, Pallàs M, Casadesus G, Lee HG, Bowser R, Raina AK, Perry G, Smith MA, Zhu X (2008) Retinoblastoma protein phosphorylation at pultiple sites is associated with neurofibrillary pathology in Alzheimer disease. Int J Clin Exp Pathol 1: 134–146.

Thal DR, Rüb U, Orantes M, Braak H (2002) Phases of A beta-deposition in the human brain and its relevance for the development of AD. Neurology 58: 1791–800.

Tighe A, Ray-Sinha A, Staples OD, Taylor SS (2007) GSK-3 inhibitors induce chromosome instability. BMC Cell Biol 8: 34.

Thomas P, Fenech M (2008) Chromosome 17 and 21 aneuploidy in buccal cells is increased with ageing and in Alzheimer's disease. Mutagenesis 23: 57–65.

Trześniewska K, Brzyska M, Elbaum D (2008) Neurodegenerative aspects of protein aggregation. Acta Neurobiol Exp (Wars) 64: 41–52.

Uberti D, Cenini G, Olivari L, Ferrari-Toninelli G, Porrello E, Cecchi C, Pensalfini A, Liguri G, Govoni S, Racchi M, Maurizio M (2007) Over-expression of amyloid precursor protein in HEK cells alters p53 conformational state and protects against doxorubicin. J Neurochem 103: 322–333.

Van Duijn CM, Clayton DG, Chandra V, Fratiglioni L, Graves AB, Heyman A, Jorm AF, Kokmen E, Kondo K, Mortimer JA (1994) Interaction between genetic and environmental risk factors for Alzheimer's disease: a reanalysis of case-control studies – EURODEM

Risk Factor Research Group. Genet Epidemiol 11: 539–551.

Venoux M, Delmouly K, Milhavet O, Vidal-Eychenié S, Giorgi D, Rouquier S (2008) Gene organization, evolution and expression of the microtubule-associated protein ASAP (MAP9). BMC Genomics 9: 406.

Vincent I, Jicha G, Rosado M, Dickson DW (1997) Aberrant expression of mitotic cdc2/cyclin B1 kinase in degenerating neurons of Alzheimer's disease brain. J Neurosci 17: 3588–3598.

Vorsanova SG, Yurov IY, Demidova IA, Voinova-Ulas VY, Kravets VS, Solov'ev IV, Gorbachevskaya NL, Yurov YB (2007) Variability in the heterochromatin regions of the chromosomes and chromosomal anomalies in children with autism: identification of genetic markers of autistic spectrum disorders. Neurosci Behav Physiol 37: 553–558.

Ward BE, Cook RH, Robinson A, Austin JH (1979) Increased aneuploidy in Alzheimer disease. Am J Med Genet 3: 137–144.

Webber KM, Raina AK, Marlatt MW, Zhu X, Prat MI, Morelli L, Casadesus G, Perry G, Smith MA (2005) The cell cycle in Alzheimer's disease: a unique target for neuropharmacology. Mech Aging Dev 126: 1019–1025.

Weihl CC, Miller RJ, Roos RP (1999) The role of beta-catenin stability in mutant PS1-associated apoptosis. Neuroreport 10: 2527–2532.

Wen Y, Yang, S-H, Liu R, Perez EJ, Brun-Zinkernagel AM, Koulen P (2007) Cdk5 is involved in NFT-like tauopathy induced by transient cerebral ischemia in female rats. Biochim Biophys Acta 1772: 473–483.

Whalley LJ, Carothers AD, Collyer S, De Mey R, Frackiewicz A (1982) A study of familial factors in Alzheimer's disease. Brit J Psychiat 140: 249–256.

Wisniewski HM, Rabe A, Wisniewski KE (1988) Neuropathology and Dementia in People with Down's Syndrome. CSH Lab Press, New York.

Wojda U, Salinska E, Kuznicki J (2008) Calcium ions in neuronal degeneration. IUBMB Life 60: 575–590.

Wu J, Basha MR, Zawia NH (2008) The environment, epigenetics and amyloidogenesis. J Mol Neurosci 34: 1–7.

Xu H, Sweeney D, Greengard P, Gandy S (1996) Metabolism of Alzheimer beta-amyloid precursor protein: regulation by protein kinase A in intact cells and in a cell-free system. Proc Natl Acad Sci U S A 93: 4081–4084.

Yang Y, Geldmacher DS, Herrup K (2001) DNA replication precedes neuronal cell death in Alzheimer's disease. J Neurosci 21: 2661–2668.

Yang Y, Mufson EJ, Herrup K (2003) Neuronal cell death is preceded by cell cycle events at all stages of Alzheimer's disease. J Neurosci 23: 2557–2563.

Yang Y. Varvel NH, Lamb BT, Herrup K (2006) Ectopic cell cycle events link human Alzheimer's disease and amyloid precursor protein transgenic mouse models. J Neurosci 26: 775–784.

Yang Y, Herrup K (2007) Cell division In the CNS: Protective response or lethal event in post-mitotic neurons? Biochim Biophys Acta 1772: 457–466.

Yurov YB, Iourov IY, Monakhov VV, Soloviev IV, Vostrikov VM, Vorsanova SG (2005) The variation of aneuploidy frequency in the developing and adult human brain revealed by an interphase FISH study. J Histochem Cytochem 53: 385–390.

Yurov YB, Iourov IY, Vorsanova SG, Liehr T, Kolotii AD, Kutsev SI, Pellestor F, Beresheva AK, Demidova IA, Kravets VS, Monakhov VV, Soloviev IV (2007) Aneuploidy and confined chromosomal mosaicism in the developing human brain. PLoS ONE. 27: e558.

Yurov YB, Iourov IY, Vorsanova SG, Demidova IA, Kravetz VS, Beresheva AK, Kolotii AD, Monakchov VV, Uranova NA, Vostrikov VM, Soloviev IV, Liehr T (2008) The schizophrenia brain exhibits low-level aneuploidy involving chromosome 1. Schizophr Res 98: 139–147.

Zekanowski C, Religa D, Graff C, Filipek S, Kuźnicki J (2004) Genetic aspects of Alzheimer's disease. Acta Neurobiol Exp (Wars) 64: 19–31.

Zhang Z, Hartmann H, Do VM, Abramowski D, Sturchler-Pierrat C, Staufenbiel M, Sommer B, van de Wetering M, Clevers H, Saftig P, De Strooper B, He X, Yankner BA (1998) Destabilization of beta-catenin by mutations in presenilin-1 potentiates neuronal apoptosis. Nature 395: 698–702.

Zhu X, Lee HG, Perry G, Smith MA (2007) Alzheimer's disease, the two-hit hypothesis: an update. Biochim Bioph Acta 1882: 494–502.

Zivkovic L, Spremo-Potparevic B, Djelic N, Bajic V (2006) Analysis of premature centromere division (PCD) of the chromosome 18 in peripheral blood lymphocytes in Alzheimer disease patients. Mech Aging Devel 127: 892–896.