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Down Syndrome Model of Alzheimer's Disease: Beyond Trisomy 21Nondisjunction

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1. Introduction

Alzheimer's disease (AD), the most common type of dementia in old age, is a complex, multifactorial neurodegenerative disorder currently affecting 35,6 million people in either familial (genetic) or sporadic form, whose prevalence is expected to quadruple worldwide by the year 2050 (Alzheimer's Disease International, 2010; Ferri et al., 2005). While genetic or early-onset AD accounts for only 5% of all cases (Cummings, 2004), 95% of sporadic or late-onset AD is attributed to the interaction between advancing age, environmental factors (Grant, et al., 2002; Tanzi & Bertram, 2001), and to the few risk-enhancing genetic polymorphisms discovered so far (Bertram & Tanzi, 2004). Autosomal dominant mutations in the amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) are linked to early-onset (familial) AD (FAD, Hardy, 2009). A combination of bio-psycho-social factors, especially if experienced at midlife, such as abnormal glucose and cholesterol metabolism, cerebral hypoperfusion, hypertension, physical and mental inactivity, diet, head injury, depression and small social networks are thought to contribute to sporadic AD initiation and development (reviewed in Flicker, 2010; Bendlin et al., 2010; Hughes & Ganguli, 2009). There is a temporal gap between clinical and pathological manifestation of Alzheimer's dementia; AD has a long prodromal phase and many clinically silent older adults are experiencing substantial pathological burden (Elias et al., 2000; Small et al., 2000). Common clinical manifestation of AD include memory impairment and dysfunctions in several cognitive domains such as language, problem solving, executive function, visuospatial skills, and others along with changes in personality and behavior (Maurer & Hoyer, 2006).

1.1 Neuropathology of Alzheimer's disease

The brain pathology of AD is characterized by extracellular deposits of the amyloid-beta peptide (Aβ), a main constituent of senile plaques, and intracellular accumulation of the hyperphosphorylated protein tau (p-tau) (Selkoe, 1999; 2001). The central hypothesis of AD, the amyloid cascade hypothesis, posits that an imbalance between Aβ production, aggregation and clearance from the brain is the initiating event in the disease process leading to synaptic loss, neuronal degeneration, inflammation, senile plaque formation and dementia (Blennow, de Leon, & Zetterberg, 2006; Hardy, 2006; Hardy & Selkoe, 2002; Lee et al., 2004; Potter et al., 2001).

The main constituent of the extracellular senile plaques is a highly neurotoxic Aβ42 isoform of Aβ protein, produced by consecutive action of two cleaving proteases, β- (BACE-1) and γ-

secretase, from a larger transmembrane protein, the Amyloid Precursor Protein (APP) (Hardy, 2009; Haass & Selkoe, 1993; Wolfe, 2003) within cholesterol rich membrane domains (Wahrle et al., 2002). A number of biochemical and genetic studies have indicated that oligomerization or polymerization of Aβ peptide driven by inflammation-induced proteins is a crucial step in AD pathogenesis (Potter et al., 2001; Hardy, 2006). Aβ42 self-aggregates and forms insoluble plaque deposits that include dystrophic neurites, activated microglia and reactive astrocytes (Itagati et al., 1989) which express a number of proinflammatory proteins (Akiyama et al., 2000; Potter et al., 2001). Furthermore, Aβ induces increased phosphorylation of the intracellular protein tau, resulting in destabilization of microtubules (MT) (Small & Duff, 2008). The evidence from transgenic mice and human studies indicates that not only extracellular, but also intracellular Aβ accumulates in diseased neurons and contributes to dementia progression by affecting the function of mitochondria, calcium ion channels and synapses (La Ferla, Green, and Oddo, 2007; Li et al., 2007). It is still unclear which toxic species of the Aβ peptide are most damaging to the neurons or whether the process of aggregation itself is detrimental to neuronal membranes.

Neurofibrillary tangles (NFTs) are the second major pathological hallmark in AD, which result from abnormally aggregated tau protein filling the intracellular space of the neurons. In AD brain, tau gets hyperphosphorylated, detaches from microtubules and forms paired helical filaments, which cause disruption in neuronal signaling, synaptic failure, impaired nutrient trafficking and neuronal death (Alonso et al., 2006; Grundke-Iqbal et al., 1986). Furthermore, oxidative damage as a consequence of free radical and reactive oxygen species (ROS) attacks has been observed in post-mortem AD brains in the form of oxidized lipids and proteins, mutated DNA, and mitochondrial damage (Floyd & Hensley, 2002). Formation of amyloid plaques and neurofibrillary tangles is not only associated with neuronal and synaptic loss, and depletion of neurotransmitters (Scheff, et al., 2006; Selkoe, 1999; 2004), but with abnormal axonal transport of key molecules and organelles important for neural cells survival and communication early in the disease process (Stokin et al., 2005; Stokin & Goldstein, 2006). Neurons, with their long axons, branched dendrites and large cell surface are especially vulnerable to energy and/or oxygen deprivation, impaired movement of molecules, and neurotoxins observed in AD pathology (Mattson & Magnus, 2006). The development of early diagnosis and successful treatments of AD will be greatly aided by a complete understanding of the pathological pathway that leads to formation of misfolded proteins, inflammation and neurodegeneration.

1.2 The Down syndrome model of Alzheimer's disease

The discovery that Down syndrome (DS) patients who live beyond the age of 30 or 40 develop neuropathology indistinguishable from the one observed in classic AD (Glenner & Wang, 1984; Olson & Shaw, 1969; Wisniewski et al., 1988) provided an important insight into AD pathogenesis, shifting the focus on nondisjunction of human chromosome 21 (HSA21) where the APP gene resides (Goldgaber et al. 1987; Neve et al., 1988; Petterson et al., 1988; Tanzi et al., 1987), and on the consequence of the gene overexpression in DS (Epstein, 1990). The fact that an extra copy of APP and subsequent 50% increase in gene dosage due to trisomy 21 in every cell of the body in DS individuals is sufficient to cause AD later in life instigated research on common biological links between AD and DS (Potter, 1991, 2008; Geller & Potter, 1999). Trisomy 21 results in altered APP processing and in an increased ratio of more amyloidogenic Aβ42 over Aβ40 (Teller et al., 1996), similar to the process observed in animal models of AD and in patients harboring mutations in FAD

genes, PS1, PS2 and APP (Haas & De Stooper, 1999; Hardy & Selkoe, 2002; Suzuki et al., 1994; Wolfe, 2003).

Several biochemical and genetic studies have shown that both sporadic and familial AD patients, including those carrying FAD mutations, are abnormal in one or more aspects of the cell cycle (Arendt et al., 1996; Geller & Potter, 1999; Potter, 1991; Varvel et al., 2008; Yang et al., 2001; 2006; Yang & Herrup, 2007; reviewed in Nagy, 2005; Obrenovic et al., 2003; Potter, 2004, 2008). The universal presence of AD pathology in DS individuals and the occurrence of an aberrant cell cycle in the brains of FAD mouse models and AD patients, led us to hypothesize that a slow accumulation of aneuploid, including trisomy 21 cells through defective mitosis and chromosome mis-segregation in central and peripheral tissues over the course of life of an individual could cause or at least help promote late-onset Alzheimer's (Potter, 1991; 2008). The extra copy of chromsome 21 that in full human trisomy of DS leads to neurodegeneration and dementia, could account for both genetic and sporadic AD, depending upon whether the chromosomal instability and mosaic aneuploidy was induced by a genetic (familial) mutation or by environmental insults. We further postulated that the microtubule disfunction likely responsible for the mitotic defects and genomic instability in AD could be linked to altered APP production and increased Aβ levels, probably affecting other aspects of neuronal physiology and function (Borysov et al., 2011; Granic et al., 2010; Potter, 2008).

The Down syndrome model and chromosome mis-segregation/microtubule disfunction hypothesis of AD made several predictions (Geller & Potter, 1999; Potter, 2008):

1. Alzheimer's patients should harbor a small number of aneuploid, including trisomy 21 cells in their somatic tissues. Altered genomic stability and development of trisomy 21 mosaicism would contribute to dementia onset and neurodegeneration but at slower pace than in DS due to the modulating effect of mostly disomic cells in the body.
2. Mutations that cause familial AD should occur in genes that encode proteins directly or indirectly involved in the cell cycle and chromosome segregation.
3. There should be alternations in microtubules, mitotic spindle apparatus and mitosis-related proteins in AD cells that could lead to aneuploidy, including trisomy 21 mosaicism.

In the past twenty years, compelling epidemiological and molecular evidence from our and other laboratories has been accumulated to test all three predictions. Together, the evidence suggests a link between pathological changes observed in the brains of DS and AD individuals and chromosomal instability and mosaic aneuploidy, including nondisjunction of HSA21 which likely contributes to dementia initiation and/or progression, with important implications for AD diagnosis and therapy.

2. The epidemiology of trisomy 21 mosaicism in Alzheimer's disease

Early epidemiological evidence indicating that chromosome mis-segregation and trisomy 21 mosaicism might be implicated in AD pathogenesis came for the studies showing a significantly higher number of Down syndrome offspring born in some families with FAD mutations (Heston et al., 1981; Heyman et al., 1983). The studies that failed to confirm this association reported to have too small sample sizes to observe statistically significant results (Amaducci et al., 1986; Chandra et al., 1987) suggesting that larger scale studies are needed to establish a connection between a higher frequency of DS children in families with genetic forms of AD. An important result that provided support for the trisomy 21 model of AD

came from a retrospective study of young mothers (aged <35) showing a five-fold greater risk of developing AD later in life compared to either older DS mothers or the general population (Schupf et al., 1994; 2001). Schupf and her colleagues interpreted this phenomenon as a novel form of 'accelerated aging'. In the light of our trisomy 21 model of AD, we postulated that the young DS mothers were most likely mosaic for chromosome 21 and had a predisposition for genomic instability, which resulted in DS progeny and their own increased risk of AD later in life. Indeed, a recent study by Migliore et al. (2006; 2009) confirmed the susceptibility to aneuploidy and trisomy 21 nondisjunction in young mothers of DS children. Case studies of patients with trisomy 21 mosaicism and no intellectual impairments of the DS type who developed AD by the age of 40 demonstrated that a small percentage of chromosomal instability is sufficient to result in early-onset AD (Hardy, et al., 1989; Ringman et al. 2008; Schapiro et al., 1989). Similarly, a slow accumulation of a low number of trisomy 21 cells over the life span may lead and/or contribute to the pathogenesis of both genetic and sporadic form of AD.

In order to directly test if Alzheimer's patients harboured mis-segregated including trisomy 21 cells, we and others have used fluorescence *in situ* hybridization (FISH), a cytogenetic technique that allows one to detect the number of copies of a particular chromosome in both metaphase and interphase cells (Ried, 1998) with great sensitivity and specificity. This method is especially suitable for poorly and non-dividing cells, or for the cells with a very low level of aneuploidy (e.g., lymphocytes). In our early study of chromosome mis-segregation in AD, we found more than twice the frequency of trisomy 21 in skin fibroblasts of AD patients ($p=0.007$) compared to age-matched controls, which was not related to the age of affected individuals (Figure 1, Geller & Potter, 1999). A small parallel study of chromosome 18 nondisjunction showed a similar increase in aneuploidy, indicating that the mitotic defect likely affected all chromosomes. The AD fibroblasts in our study included those with sporadic (late-onset) AD and those carrying a familial AD mutation in PS1, PS2, or APP which are now known to cause early AD onset and altered APP processing (e.g., Li et al., 1995; Schellenberg et al., 1993; Rogaev et al. 1995).

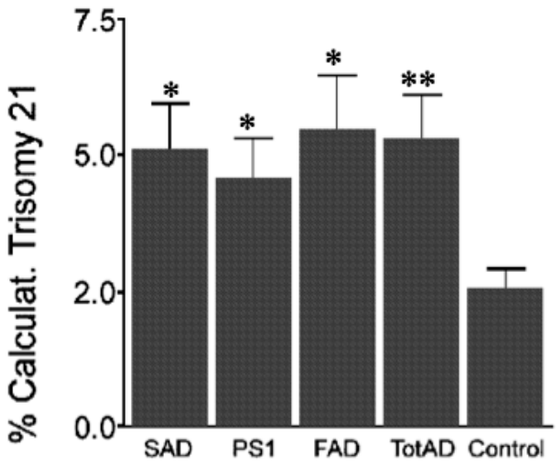

Fig. 1. AD fibroblasts, including those with PS1 or PS2 mutation (FAD) and those of sporadic origin (SAD) showed increased trisomy 21, *$p < 0.01$; **$p < 0.001$. (Used with permission from Geller & Potter, 1999, *Neurobiology of Disease).*

Trisomy 21 mosaicism and chromosome mis-segregation have also been observed among peripheral blood lymphocytes (Migliore 1997; 1999; Trippi et al., 2001), buccal cells (Thomas & Fenech, 2008), and neurons from sporadic AD patients (Arendt et al., 2010; Iourov et al., 2009; Mosch et al., 2007; Yang et al., 2001). Specifically, AD brains harbor up to 35% of hyperploid, including trisomy 21 and other tetrasomic neurons which are detectable at mild stages of the disease before any evident neuronal loss (Arendt et al., 2010; Iourov et al. 2009). The presence of tetrasomic neurons as explained by some reseachers, may indicate re-entry into an incomplete cell cycle and selective vulnerability to cell death of post-mitotic, mosaic neurons as an important pathogenic event in AD (Arendt et al., 2010; Obrenovich et al., 2003; Varvel et al., 2008; Vincent et al., 1996; Yang & Herrup, 2007). In our studies of AD mosaicism (Boeras et al., 2008; Geller & Potter, 1999; Granic et al., 2010), we failed to observe statistically significant induction of tetrasomic cells in sporadic and familial models of AD, but rather pronounced accumulation of trisomy cells in both peripheral and brain tissues. A larger scale cytogenetic autopsy and biopsy study, preferably at the single cell level is needed to further elucitate the type and extent of pathologic genetic instability in AD and other neurodegenerative diseases.

In summary, several laboratories confirmed that trisomy 21 mosaicism is commonly associated with AD. Moreover, there is an indication of a dose response effect in which full trisomy 21 in DS individuals elicits AD-like pathology by age 20 and by middle age in familial AD and even later in sporadic Alzheimer's patients, who also belonged to the trisomy 21 mosaic group found to have an increased frequency of DS children before the age of 35. The recent discovery of families that develop early-onset inherited AD only because the APP gene on one chromosome 21 is duplicated (McNaughton et al., 2010; Rovelet-Lecrux et al., 2006; Sleegers et al., 2006) indicates that the extra copy of the APP gene and consequent overproduction of Aβ peptide is the likely cause of AD in both Down syndrome and trisomy 21 mosaic individuals.

2.1 Mitotic defects in Alzheimer's disease

Along with the studies described above, separate lines of investigations provided independent evidence that other mitotic defects and mitosis-specific proteins may be present in the cells of AD patients (reviewed in Potter, 2004). For instance, the mitotic spindles in dividing AD cells exhibit abnormalities and susceptibility to premature centromere division (PCD) and micronucleation upon chemically induced (e.g., colchicines) microtubule damage (e.g., Fitzgerald et al., 1986; Potter et al., 1995; Trippi et al., 2001). The event of PCD, in which individual sister chromatids are separated by a clear gap and not connected at the centromeres, has been observed in patients prone to genomic instability and chromosome mis-segregation, and recently confirmed in neurons of individuals with sporadic AD (Spremo-Potparević et al., 2008).

Further evidence linking cell cycle defects with AD pathogenesis came for the finding that both APP and the microtubule-stabilizing tau protein get increasingly phosphorylated during mitosis (Suzuki et al., 1994; Pope et al., 1994; Padmanabhan et al., 2011). Also, phospho-tau and other mitosis-specific phospho-proteins are overexpressed in AD but not in normal brains (e.g., Arendt et al., 1996; Vincent et al., 1996; Nagy et al., 1997), indicating a cycling stage of AD neurons. The idea of unscheduled cycle in fully differentiated neurons challenged the dogma of their post-mitotic nature and the inability to replicate (Rakic, 1985). To date, the evidence drawn from animal models of AD and autopsy studies of human brains indicates that reactivation of the cell cycle and DNA duplication (e.g., Yang et al.,

2001) in the vulnerable population of AD neurons may present a fundamental initiator of AD pathogenesis (Nagy, 2005; Vincent et al., 1996; Varvel et al., 2008; Yang & Herrup, 2007; Yang et al., 2006) present before deposition of fibrilar Aβ and neuronal death, and could also lead to chromosome mis-segregation and aneuploidy.

3. Presenilin and APP mutations induced aneuploidy

The finding that fibroblast cultures from patients carrying autosomal dominant mutations in the PS1, PS2 or APP gene harbour chromosomal instability and trisomy 21 mosaicism provided the first indication that FAD genes are likely to be involved in mitosis and chromosome mis-segregation, or to be associated with structures and proteins of the cell cycle (Geller & Potter, 1999).

Indeed, we and others have confirmed a major location of PS1 and PS2 proteins in dividing cells in the centromeres, the nuclear envelope, and the kinetochores during interphase (Li et al., 1997; Honda et al., 2000). Further support for a mitotic function of presenilins comes from studies showing inhibition of the cell cycle (Janicki & Montero, 1999) and increased sensitivity to apoptosis (Vito et al., 1996; Wolozin et al., 1996) in the cells carrying a mutated PS gene. Furthermore, polymorphisms in the PS1 gene have been associated with an increased risk of AD (Wragg et al., 1996; Higuchi et al., 1996; Scott et al., 1996) and with an increase of DS offspring via a meiosis II defect (Petersen et al., 2000; Lucarelli et al., 2004) as a more direct confirmation of PS1 involvement in the cell cycle.

Further research should be directed at discovering the mechanism by which the mutant presenilins influence chromosome segregation. One possibility supported by the data collected so far points to inability of altered presenilin proteins to properly link the chromosomes to the nuclear envelope and to release them at the appropriate time during mitosis, which may lead to chromosome mis-segregation and other cell cycle abnormalities. Another possibility discussed further below links PS mutations to altered processing of APP and increased production of neurotoxic Aβ42 as a likely effector molecule responsible for cell cycle defects, including mitotic spindle abnormalities and chromosome mis-segregation (Boeras et al., 2008; Borysov et al., 2011, Granic et al., 2010). Similarly, APP is also found to localize to the centrosomes and nuclear membrane in dividing cells (Nizzari et al., 2007; Zitnik et al., 2006), and to get increasingly phosphorylated during the cell cycle (Padmanabhan et al., 2011).

In a series of *in vivo* and *in vitro* experiments we investigated the role of mutated PS1 and APP genes and their proteolytic product, the Aβ peptide in chromosome mis-segregation and trisomy 21 mosaicism. All assays, tissues and cells from transgenic mice carrying AD mutations and the cells transfected with FAD genes or treated with Aβ peptide yielded comparable results: overexpression of FAD genes *in vivo* and *in vitro* and exposure to Aβ peptide induced chromosome instability and trisomy 21 mosaicism through several defects in mitotic spindle apparatii and dysfunction of microtubule assembly (Boeras et al., 2008; Borysov et al., 2011; Granic et al., 2010; Potter et al., 2008).

3.1 Presenilin and APP mutations induced aneuploidy in transgenic mice

We asked whether chromosome mis-segregation and trisomy 21 mosaicism observed in human fibroblasts with PS1 or APP mutations could be mimicked in peripheral and brain tissues of FAD-transgenic mice. For example, whole brains from PS1 (M146l and M146V) and APP (V717) mutant mice and non-transgenic littermates were processed to yield

primary cultures. The isolated neurons were hybridized with a mouse chromosome 16 BAC probe (Kulnane et al., 2002), followed by immunocytochemistry to stain for neurons. Most cells were disomic with two copies of chromosome 16; while the neurons from PS1 mutant and PS1 knock in mice exhibited up to 4% of trisomy 16 (data not shown, Boeras et al, 2008), the APP-transgenic mice had about 6.5% of trisomies (Figure 2, Granic et al., 2010).

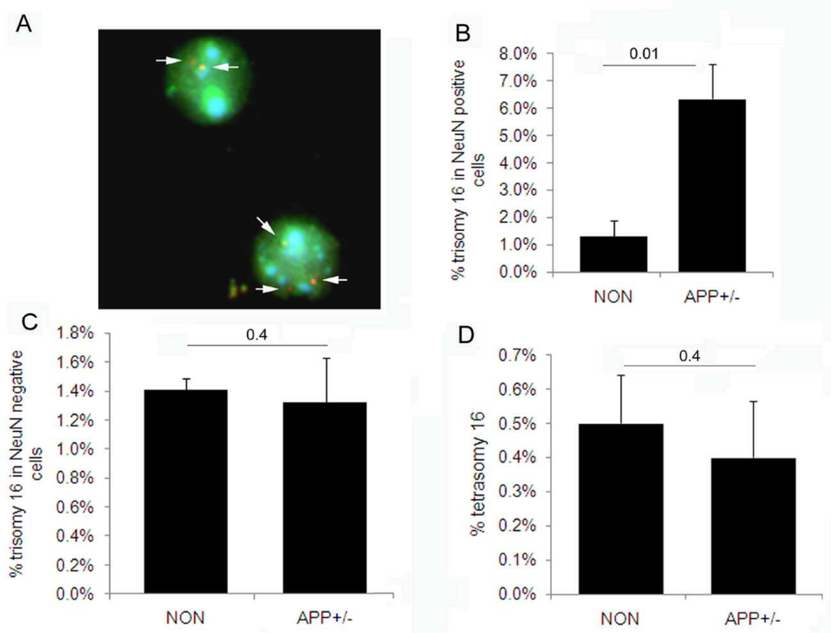

Fig. 2. Quantitative FISH analysis revealed significantly higher levels of trisomy 16 in APP mice (A & B) compared to controls but no tetrasomy (D) and no induction of aneuploidy in non-neuronal cells (C). (Used with permission from Granic et al., 2010, *Molecular Biology of the Cell*).

3.2 Presenilin and APP mutations induced aneuploidy in transfected cells

To determine whether the aneuploidy observed in FAD-transgenic and knock-in mice was caused directly by mutated genes and not by some other factors, parallel cultures of the hTERT-HME1, an immortalized primary mammary epithelial cell line with a stable karyotype (Clontech) were transiently transfected with WT-PS1, mutant PS1 (M146L), mutant APP (K595N/M596L and V642I or V717) and control empty vector (pcDNA3 and paG3). FISH was used to assess the levels of aneuploidy for chromosome 21 and 12. Overexpression of FAD-genes induced between 2-3% of trisomy 21 and/or trisomy 12 (Boeras et al., 2008; Granic et al., 2010), and about 30% of total aneuploidy in metaphase cells within 48 hours (Boeras et al., 2008). These results indicated that an aneugenic effect of FAD-mutations likely affected all chromosomes with random gains and losses of whole chromosomes, and that chromosome mis-segregation was not restricted only to the cells expressing mutated genes, but extended to nearby, non-transfected cells. We hypothesized that Aβ peptide itself found at increased levels in both familial and sporadic AD might be the probable effector molecule interfering with mitosis and chromosome segregation (Boeras et al., 2008; Potter, 2008). Lastly, immunocytochemistry of PS1-transfected cells revealed several abnormalities in the mitotic spindles, with disarrayed microtubules, multiple

centosomes and lagging chromosomes as the most prominent spindle malformations (Boeras et al., 2008).

3.3 Aβ induced aneuploidy and the role of tau

Sequential cleavage of the APP protein with β- and presenilin/γ-secretase enzymes yields more amyloidogenic Aβ42 peptide as a central event in AD pathogenesis. We proposed to test the role of Aβ in genomic instability and trisomy 21 induction. Led by our initial observation that more cells became aneuploid than are transfected and express FAD genes, we examined the aneugenic effect of Aβ peptide in culture. hTERT-HME cells treated with 1μM Aβ40 and Aβ42 develop more than 20% aneuploid metaphases and about 2% trisomy 21 and 12 cells within the 48 hours of exposure compared to 6% and less than 1% of the cells treated with various control peptides (Figure 3, Granic et al., 2010). These results indicated that AD might be a self-propagating disorder in which the product of FAD mutations and trisomy 21, the Aβ peptide, further induces chromosome segregation and generation of trisomy 21 cells.

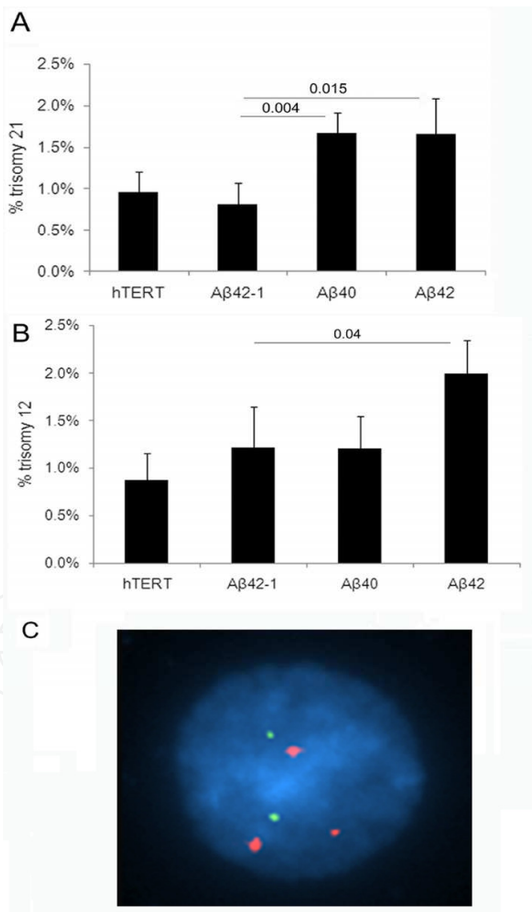

Fig. 3. Quantitative FISH analysis with a dual color probe revealed an increased induction of trisomy 21 (SpectrumOrange, Vysis) and trisomy 12 (SpectrumGreen) in Aβ treated hTERT-HME cells (A-C). (Used with permission from Granic et al., 2010, *Molecular Biology of the Cell*).

To investigate the mechanism by which Aβ exerts its aneugenic effect on dividing cells, we analyzed the peptide's other toxic activities especially those related to microtubule function. Several lines of investigation have indicated that Aβ induces and requires downstream changes/defects in microtubules (MT) to exert its neurodegenerative activity. Numerous *in vitro* and *in vivo* studies have shown that Aβ induces phosphorylation of tau (e.g., Small & Duff, 2008), and that Aβ toxicity depends on the presence of tau (Rappaport et al., 2002). Therefore, we investigated the role of tau in Aβ induced aneuploidy. Splenocytes prepared from normal, Tau+/-, Tau -/- mice were treated with Aβ peptide and analyzed for aneuploidy 48 hours later. Knocking out one or even more effectively both copies of Tau induced up to 5% aneuploidy (trisomy 16). However, the Aβ aneugenic effect was greatly attenuated in the cells lacking Tau but not in normal cells, indicating that Aβ induced chromosome mis-segregation requires tau protein and disrupts normal tau-stabilizing microtubule function. In a series of studies, Borysov et al. (2011) have shown that Aβ42 peptide added to *Xenopus* egg extracts impairs the structure and stability of mitotic spindles, and inhibits three motor kinesins, Eg5, KIF4A, and MCAK, required for normal mitotic spindle function and proper chromosome segregation.

Recently, we have shown that overexperssion of APP prevents the localization of low density lipoprotein receptor (LDLR) from the Golgi to the cell membrane (Abisambra et al., 2010). This latest finding led us to hypothetize that neurons exposed to Aβ in AD brains may also fail to localize other key receptors to the cell membrane, including those for neurotrophins and neurotransmitters, causing neuronal disfunction and dementia. Future studies are under way to confirm if the interference with microtubule function by Aβ will cause defects in neuroplasticity through mis-localization of the receptors away from the plasma membrane, as well as contributing to defective neurogenesis leading to dysfunctional, aneuploid, including trisomy 21 neurons prone to Aβ overproduction and neurodegeneration.

4. How trisomy 21 mosaicism may lead to Alzheimer's disease

Several potential mechanisms could explain how trisomy 21 mosaicism could lead to AD (Potter, 1991; 2004; 2008). For instance, aneuploidy cells might be prone to cell death and neurodegeneration (Arendt et al., 2010), similar to cortical neurons in DS brains that undergo spontaneous apoptosis (Busciglio & Yankner, 1997). Apoptosis could also indirectly affect APP processing and Aβ levels in mosaic AD brain. The support for the latter hypothesis comes from the finding that embryonic DS brains and adult sera contain a higher ratio of neurotoxic Aβ42 over Aβ40 peptide (Teller et al., 1996). Also, trisomy 21 microglia overexpress inflammatory proteins and begin an inflammatory cascade that promotes Aβ fibrilization (Potter et al., 2001). Finally, aneuploidy in AD may arise from a defect in microtubule function which may lead to poor protein, neurotransmitters and nutrient trafficking (Cash et al., 2003). Trisomy 21 may be both a cause and an effect of microtubule dysfunction generating a feed-forward loop further promoting AD progression.

5. Implications of the trisomy 21 model of Alzheimer's disease for diagnosis and therapy

The mechanistic implication of the results discussed in this review is that an early step in Alzheimer's disease pathogenesis may be the development of genomic instability and

trisomy 21, contributing to progression of dementia. The search for more effective diagnoses should take into account the events of mitotic defects in peripheral and central tissues of individuals at risk. Chromosome analysis and detection of low levels of trisomy 21 in skin fibroblasts or buccal cells in patients during the pre-clinical phase of dementia could be a potential diagnostic test. Another implication of the data presented above that trisomy 21 in AD may be the initiating event in disease pathogenesis also suggests new approaches to treatments (Potter, 2004). For example, drugs that would repair the mitotic defects and strengthen the fidelity of the chromosome segregation could be searched for and used prophylactically. Further, aneugenic environmental agents that cause chromosome instability could be identified and counteracted with drugs that restore genomic homeostasis. Another more difficult but equally effective approach to therapy would be to detect and remove mis-segregated cells from the body by exploiting their unique cell biology and/or gene expression.

To summarize, the results from several laboratories over the past twenty years have shown that Alzheimer's patients are prone to genomic instability accumulating about 2-3 fold more trisomy 21 cells throughout the body compared to age matched healthy controls. The precise mechanism by which these abnormal cells arise during the life span of an individual and how or whether they contribute to disease initiation and progression are subjects of active investigation. The better understanding of these novel findings has the potential to contribute to the development of future diagnoses and therapies for Alzheimer's disease.

6. Summary

Convincing epidemiological and molecular evidence has been accumulating that link pathological changes observed in the brains of both Down syndrome individuals and neurodegeneration in Alzheimer's disease to chromosomal instability and trisomy 21 mosaicism. The results from several laboratories indicate that errors in mitosis, specifically mis-segregation of somatic chromosomes in peripheral and brain tissues of AD patients may play an important role in both early (familial) and late (sporadic) onset of disease. Here, we proposed a unifying hypothesis for Alzheimer's and Down syndrome neurodegeneration—development of a mosaic population of aneuploid, including trisomy 21 cells and alternation in genomic stability may lead to classic AD neuropathology observed in both diseases. The evidence for this hypothesis include: a) cells from familial and sporadic AD patients exhibit mis-segregated, including trisomy 21 cells in brain, blood, mucosa and skin, and harbour abnormalities in several aspects of the cell cycle that may contribute to aneuploidy and neurodegeneration; b) overexpression of mutated Alzheimer's genes, presenilin 1 and APP, in cellular and transgenic mouse models induce aneuploidy, including trisomy 21; and c) Aβ peptide is the likely effector molecule responsible for disruption of proper functioning of microtubules and mitotic spindle integrity leading to mitotic defects and apoptosis. The possibility that many cases of Alzheimer's disease are mosaic for trisomy 21 opens new approaches for diagnosis and therapy.

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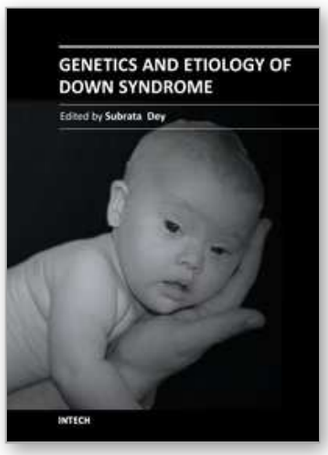

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This book provides a concise yet comprehensive source of current information on Down syndrome. Research workers, scientists, medical graduates and paediatricians will find it an excellent source for reference and review. This book has been divided into four sections, beginning with the Genetics and Etiology and ending with Prenatal Diagnosis and Screening. Inside, you will find state-of-the-art information on: 1. Genetics and Etiology 2. Down syndrome Model 3. Neurologic, Urologic, Dental & Allergic disorders 4. Prenatal Diagnosis and Screening Whilst aimed primarily at research workers on Down syndrome, we hope that the appeal of this book will extend beyond the narrow confines of academic interest and be of interest to a wider audience, especially parents and relatives of Down syndrome patients.

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