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Is the time dimension of the cell cycle re-entry in AD regulated by centromere cohesion dynamics?

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Abstract

Chromosomal involvement is a legitimate, yet not well understood, feature of Alzheimer disease (AD). Firstly, AD affects more women than men. Secondly, the amyloid- β protein precursor genetic mutations, responsible for a cohort of familial AD cases, reside on chromosome 21, the same chromosome responsible for the developmental disorder Down's syndrome. Thirdly, lymphocytes from AD patients display a novel chromosomal phenotype, namely premature centromere separation (PCS). Other documented morphological phenomena associated with AD include the occurrence of micronuclei, aneuploidy, binucleation, telomere instability, and cell cycle re-entry protein expression. Based on these events, here we present a novel hypothesis that the time dimension of cell cycle re-entry in AD is highly regulated by centromere cohesion dynamics. In view of the fact that neurons can re-enter the cell division cycle, our hypothesis predicts that alterations in the signaling pathway leading to premature cell death in neurons is a consequence of altered regulation of the separation of centromeres as a function of time. It is well known that centromeres in the metaphase-anaphase transition separate in a non-random, sequential order. This sequence has been shown to be deregulated in aging cells, various tumors, syndromes of chromosome instability, following certain chemical inductions, as well as in AD. Over time, premature chromosome separation is both a result of, and a driving force behind, further cohesion impairment, activation of cyclin dependent kinases, and mitotic catastrophe, a vicious circle resulting in cellular degeneration and death.

Keywords

Alzheimer disease; aneuploidy; cell cycle; chromosome

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Introduction

The canonical markers of Alzheimer disease (AD) are the extracellular senile plaque, an aggregate of amyloid- β peptides, and the intracellular neurofibrillary tangle, a mass of irregularly folded proteins composed mainly of highly phosphorylated tau protein. The causes and consequences of both amyloid- β and tau accumulation are a primary focus in the field. In particular, the relationship between tau and amyloid on other mechanisms known to be involved in disease pathogenesis has garnered considerable attention. In this regard, changes in cell cycle dynamics appear to be centrally involved. Indeed, the intracellular accumulation of highly phosphorylated tau is linked to the cell cycle and cell cycle dependent kinases.

Among others, cell senescence, oxidative stress, and de-regulated apoptosis are important factors in the pathogenesis of AD and are influenced by aberrations in cell cycle dynamics and, in particular, telomere length [1,2]. Notably, the link between cell cycle related events and apoptosis is becoming increasingly recognized in neurodegeneration [3] and it is apparent from studies using neuronal cultures that amyloid- β -mediated cell death, by apoptosis or similar mechanisms [4], only occurs if cells re-enter into a mitotic state [5].

That central nervous system (CNS) neurons in adults are in a terminal stage of differentiation is a longstanding dogma in neuroscience, notwithstanding neurogenesis in select neuronal populations [6]. However, the addition of the rather infrequent neuronal binucleation events [7], together with an ectopic re-expression of a variety of cell cycle markers, provides compelling evidence that neurons in AD re-enter the cell division cycle and circumvent conventional dogma [4,7–20]. In mammalian cells, re-entry into the cell division cycle depends on extracellular signals, namely on the balance between mitogenic stimuli and differentiating factors [4,21,22]. Sequential expression, activation and degradation of cyclin/cyclin dependent kinase complexes drive the cell cycle, while their regulation is achieved via mechanisms of transcription, phosphorylation, proteolysis, and association with cyclin dependent kinase inhibitors (CDKIs) [23]. G₀/G₁ phase transfer in the cell cycle is triggered by the presence of cyclin D/CDK4 and CDK6 complex [24]. When DNA replication is completed, the cyclin A/CDK2 complex enables transition from the S to the G₂ phase (S/G₂) of the cell cycle. For the cell to enter the G₂ phase of mitosis (G₂/M), degradation of cyclinA/CDK2 complex and expression of cyclin B which activates CDK2 must take place [24].

It has been demonstrated that various mitogenic signals can cause cell cycle re-entry of neurons in the CNS of AD patients [4,5] and loss of synaptic connections may be one of these factors. Also, levels of plasma homocysteine, which are believed to be a common risk factor for both AD and vascular disease, are a possible mitogenic signal. On the other hand, there is evidence that amyloid- β itself is mitogenic in cultured neurons [25,26]. Also, the fact that AD affects twice as many women than men, and women develop AD mainly after the menopause, indicates that hormonal factors may play an important role in the loss of the differentiated phenotype in neurons [27,28]. Additionally, cerebral hypoxia can also trigger neuronal cell cycle re-entry [29].

Using a scientific approach quite different from approaches used to date, work done on the alterations of centromere dynamics in interphase nuclei of neuronal cells and peripheral blood lymphocytes of AD patients [30–32] have confirmed not only that these cells undergo mitosis but that the temporal dynamics of centromeres are highly altered.

The centromere plays a fundamental role in accurate chromosome segregation during mitosis and meiosis in eukaryotic cells functioning in sister chromatid adhesion and separation, microtubule attachment, chromosome movement and mitotic checkpoint control.

The sequential separation and segregation of centromeres is genetically controlled and it is apparent that this sequence of temporal order is altered in AD, i.e., centromeres divide prematurely. This aberrant division is called premature chromosome separation (PCS) and is seen as a manifestation of genome instability leading to aneuploidy in aging, AD and other chromosome instability syndromes. Based on our current knowledge of PCS, we can postulate that there is increased instability of neuronal cells that over time leads to a mitotic catastrophe and premature cell death (Figure 1). Mitotic catastrophe, recognized as one of the earliest events in neuronal degeneration, may, in fact, be sufficient to initiate the neurodegenerative cascade [33].

Chromosomes and the Fourth Dimensional Control of the Cell Cycle

For the cell division cycle to proceed flawlessly, it has to be regulated in both time and space [34,35]. This is achieved by the synthesis and destruction of specific cell cycle regulators at very specific times in the cell cycle. In the spatial dimension, the cell coordinates dramatic reorganizations of the subcellular architecture at the start of, and the exit from, mitosis, largely through protein kinases, cyclin dependent protein kinases which are members of a conserved family of serine/threonine protein kinases (CDK) which need to bind to their partner cyclin. Phosphorylation and dephosphorylation is achieved by different kinases (CAK) and phosphatases (KAP), which are localized to specific subcellular structures. Spatial organization of the cell cycle regulators are fundamentally important to the temporal control of the cell cycle [34,36]. Chromosomes in the interphase occupy compact discrete territories. The specific structure and location of these territories may be specific for both cell type and stage of the cell cycle [37]. Also, the centromere and telomere distribution patterns in interphase nuclei appear not only to be dependent on the cell type but on the stage of the cell cycle and may be influenced by the stage of differentiation. All human chromosomes at prometaphase are aggregated briefly into a single, wheel shaped ring known as the chromosome rosette. Cells exhibit consistent patterns of chromosome homologues that are situated on the opposite sides of the rosette and are preserved through the rest of the cell cycle. In addition, data suggests that chromosomes on the rosette are separated into two distinct groups of 23 different homologues, with each haploid set derived from one parent. The rosette shows an anti-parallel arrangement.

Thus, centromere interconnection in the rosette eliminates randomness of chromosome congression movements towards forming the metaphase plate, ensuring that all chromosomes are incorporated into the chromosome rosette by the end of prometaphase, and thus ensuring the remarkable success rate of mitosis. But the chromosomes are not only spatially organized, i.e., chromosomes once placed at the metaphase plate go into a time regulated process called sequential separation of centromeres. They separate and segregate in a time-dependent order and at an exact time in the cell cycle. The first human chromosome to separate is chromosome 18 and thereafter, in an ordered sequence, chromosomes 17, 2, 10 and 12 follow the separation of chromosome 18. Those separating last belong to chromosomes 21, 22, 13, 14 and 15. This sequence can be deregulated in ageing cells, AD patients, various tumors, chromosome instability syndromes and by chemical induction [32,38–42]. Phenotypically, PCS is characterized by chromatids and centromeres distinctively separated before usual time (Figure 2).

The mechanism that controls the sequence of centromere separation as a function of time is not fully understood. One of the reasons is that the time dimension concerning centromere dynamics is complex, i.e., not only is there a sequential order of centromere separation in the metaphase-anaphase transition but also there is a *time-dependence of the replication of centromere regions in homologue chromosomes*. As such, two chromosomes never replicate at the same time. Moreover, using chromosomes with two or more centromeres, Vig and colleagues [39] found that only one centromere is active and the other are inactive (mouse

chromosomes with 8 centromeres). Still, the inactive centromere was the first to replicate and to separate prematurely. These authors proposed that the replication pattern of homologue centromeres may influence the outcome of the time sequence in separating chromosomes. Similarly, Litmanovitch and colleagues showed an association between replication timing of the α -satellite centromere sequences for the 10, 11, 17 and X chromosome and their centromeric function [43]. Chromosome pairs whose homologue loci replicated highly synchronously showed low rates of aneuploidy whereas chromosome pairs with a slightly asynchronous replication pattern (i.e., short intervals between early and late replicating loci) showed intermediate rates of aneuploidy, and chromosome pairs exhibiting asynchrony with long time intervals between early and replicating loci showed the highest rate of aneuploidy [44]. Also, Ameil and colleagues showed that replication asynchrony increases in women at risk for aneuploidy offspring [44] and there is a relationship between loss of replication control, centromere dysfunction and predisposition to non-disjunction [45,46]. How serious changes in time regulation can be is perhaps best exemplified by primary repeated non-disjunction of chromosome 21, X and 18 by PCS in women clinically normal and who have Down offspring having twice the chance to develop AD [47–49]. Notably, there is a preferential susceptibility of chromosomes X, 18 and 21 to aneuploidy in aged and AD subjects [30,32,38,42–44,46, 50].

Research has shown that PCS appears considerably earlier than previously presumed, i.e., in the interphase of the cell cycle [30,32]. The fluorescent *in situ* hybridization (FISH) method applied to the centromere region of the X chromosome in interphase nuclei of lymphocytes from peripheral blood in AD patients demonstrated that PCS appears considerably before mitotic metaphase, directly after completion of DNA replication in G₂ phase of the cell cycle [30–32]. Using FISH, an analysis of PCS of the X chromosomes was made of histopathologic slides of neurons from the frontal cerebral cortex, in a group of sporadic AD patients and in age-matched controls [50]. The presence of PCS on the X chromosome was verified in all analyzed individuals. The group of AD sporadic patients had an average frequency of this alteration of $8.60 \pm 1.81\%$ compared to the control group with an average frequency of $2.96 \pm 1.20\%$, showing a highly statistical significance ($P < 0.01$). One of the first reports applying the FISH method for the analysis of centromeric regions of chromosomes 18 and 21 in hippocampal interphase nuclei pointed to an ultimate death of these cells as a consequence of genetic disbalance caused by tetraploidy of their genome [36]. However, there are no cells in mitosis [7]; therefore, it is likely that in AD, neuronal cells pass the G₁-S phase, enter the G₂ phase, and then are on the road to premature death.

Is Centromere Cohesion the Key to Understanding AD Neuronal Instability?

The temporal instability in neuronal and peripheral blood cells in AD indicates that cohesion is altered by an unknown mechanism. The centromere and chromatid arms are held by a protein called cohesin [51]. Cohesin contains two SMC subunits, Smc1 and Smc3, and two non-SMC subunits, Scc1(Rad21) and Scc3. Cohesin is loaded onto chromosomes before S phase and establishes cohesion between the duplicated chromosomes (sister chromatids) during DNA replication. This regulated linkage is released in preparation for chromosome segregation through a well-defined mechanism that involves the phosphorylation and proteolytic cleavage of the non-SMC cohesin subunit Scc1/RAD 21. By contrast, the mechanisms that underlie the loading and assembly of cohesin onto chromosomes are poorly understood [51].

The cohesion complex is now seen as a way for centromeres to influence expression [52], regulation of time directly through the clock gene paralogue TIM-1 (Timeless 1) [53], homologue repair [54] and check point control [55]. AD patients show central and peripheral time dysfunctionality, leading to increased aneuploidy [50] and to neuronal cell death.

Using a hybrid model for exploring chromosome 21 instability and RNAi processing, Fukagawa and colleagues showed that Dicer-deficient cells express mitotic defects and that many cells died in interphase by apoptosis [55]. Cells died of mislocalization of cohesion protein RAD 21 with chromosomes expressing PCS and BUB 1 inactivation [55]. Inactivation of BUB 1 shows that the check point pathway has a defect. If the mitotic checkpoint is defective, the cells should progress through anaphase. However, cells cannot enter anaphase because the sister chromatids and centromeres have separated prematurely and the chromosomes are not aligned at the metaphase plate leaving the cells with multiple spindles.

A Probable Centromere Instability Induced by a Kinase

RNAi processing is important to the regulation of the temporal order centromere separation and segregation. CDKs that are involved in a variety of important regulatory pathways in eukaryotic cells, including cell-cycle control, apoptosis, neuronal physiology, differentiation and transcription are also involved in RNAi processing and cohesion. Can we link altered cohesion, PCS-trait in AD and CDKs?

The 110-kDa protein isoform of cyclin-dependent kinase 11 (CDK11^{p110}), the major protein kinase isoform, is expressed throughout the cell cycle and is involved in transcriptional regulation and RNA processing and the 58-kDa protein isoform of cyclin-dependent kinase 11 (CDK11^{p58}) is specifically expressed in the G₂/M phase of the cell cycle. Previous studies have shown that minimal overexpression of CDK11^{p58} in Chinese hamster ovary (CHO) cells results in aneuploidy, increased numbers of cells that maintain postmitotic bridges or midbodies, and apoptosis [56]. CDK11^{p58} kinase also plays a crucial role in mitotic progression and is required for the maintenance of sister chromatid cohesion and for the completion of mitosis in human cells [56,57]. Depletion of CDK11^{p58} kinase enhanced G₂/M population of mitotic arrest of cells containing prematurely separated sister chromatids. The extent of these abnormalities is correlated with the level of CDK11 depletion. Also, overexpression of the RNAi-resistant form of CDK11^{p58-GFP}, but not the RNAi-sensitive form, reduced the number of cells with prematurely separated sister chromatids by 75%. The presence of prematurely separated sister chromatids and centromeres after downregulation of CDK11^{p58} suggests that this kinase plays a role in the maintenance or protection of chromosome cohesion. Both kinases, by a caspase-dependent pathway can initiate apoptosis [58].

In conclusion, in AD, the gross change in the neurons and the peripheral blood lymphocytes perceived as centromere division due to possible defects in processing centromere cohesion and how these defects may relate to time, is a question which warrants further investigation. Our hypothesis, that alteration of temporal order in AD has a fundamental impact on the neuronal cell cycle re-entry and consequently premature cell death by mitotic catastrophe, points to future directions of research.

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Figure 1.

A schematic representation of hypothetical time and space alterations of critical events in a AD cell trying to enter the cell cycle. Once cell cycle reentry is initiated, the neuronal cell undergoes ectopic expression of cyclins and cyclin dependent kinases, activation of the G2/M checkpoint, cohesion impairment, premature centromere division and mitotic catastrophe. Over time, this vicious circle accelerates the ageing processes in AD leading to dementia, cognition decline, and eventually cell death.

Figure 2.
Normal metaphase (A) and a metaphase showing premature centromere division (B).