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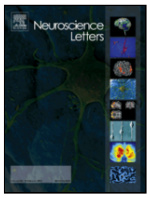

Minireviews

Aging and Alzheimer´s disease connection: Nuclear Tau and lamin A

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ABSTRACT

Age-related pathologies like Alzheimer`s disease (AD) imply cellular responses directed towards repairing DNA damage. Postmitotic neurons show progressive accumulation of oxidized DNA during decades of brain aging, which is especially remarkable in AD brains. The characteristic cytoskeletal pathology of AD neurons is brought about by the progressive changes that neurons undergo throughout aging, and their irreversible nuclear transformation initiates the disease. This review focusses on critical molecular events leading to the loss of plasticity that underlies cognitive deficits in AD. During healthy neuronal aging, nuclear Tau participates in the regulation of the structure and function of the chromatin. The aberrant cell cycle reentry initiated for DNA repair triggers a cascade of events leading to the dysfunctional AD neuron, whereby Tau protein exits the nucleus leading to chromatin disorganization. Lamin A, which is not typically expressed in neurons, appears at the transformation from senile to AD neurons and contributes to halting the consequences of cell cycle reentry and nuclear Tau exit, allowing the survival of the neuron. Nevertheless, this irreversible nuclear transformation alters the nucleic acid and protein synthesis machinery as well as the nuclear lamina and cytoskeleton structures, leading to neurofibrillary tangles formation and final neurodegeneration.

1. Introduction

Aging is a universal and holistic biological process underlying the declining health of cells and tissues. This damage leads to irreversible systemic dysfunction bringing about diseases and finally death. Four primary causes within the cellular origin of aging have been established: genomic instability, telomere attrition, epigenetic alterations, and loss of proteostasis [1]. Three out of them directly affect nuclear chromatin structure and function [2], and they are related to cumulated DNA damage throughout cellular life [3].

The genesis of highly prevalent pathologies such as Alzheimer´s disease (AD) and cancer is closely related to aging [4]. Decades of research have succeeded in the treatment of some types of cancer, but minimal achievements have been reached concerning effective AD therapies [5]. In this respect, AD research has been overwhelmingly focused on aberrant neuronal cytoplasm and neuropile alterations related to tau and β-amyloid misfolded proteins, respectively [6]. In this review, we analyze the progressive changes that hippocampal neurons undergo throughout aging and the irreversible nuclear transformation that originates the cytoskeletal pathology in AD. The discussion is centered on the role of nuclear lamin (NL) and tau protein.

2. Neuronal aging and nuclear lamin dysfunction in AD

2.1. Nuclear lamin and Alzheimer´s disease

Nuclear lamin (NL) is a flexible multimeric protein network conforming the nuclear structural scaffold. It connects the nucleoskeleton with the cytoskeleton through a platform of intermingled proteins called A, C, B1, and B2 lamins, each of them with different mechanical properties [7]. These proteins spread from the nuclear periphery throughout the nucleoplasm, creating an anchoring net for chromatin [8]. Not every cell has a NL consisting of all four lamin proteins, but each cellular type has a specific composition and organization of them [9–11]. The degree of stiffness and flexibility of NL required by each cell is conferred by the specific array of lamins [12–14]. NL regulates genic expression since it is directly or indirectly related to DNA replication, transcription, and reparation, as well as to the control of the cell cycle. In consequence, NL is intimately related to basic and complex biological processes such as development, differentiation, and aging [15].

Lamin B1 and B2 are the main components of human neuronal NL, although a minor contribution of Lamin C cannot be discarded [16].

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The constant presence of Lamin B1 allows the NL to maintain the nuclear shape [14,7]. Nevertheless, increased expression of Lamin B2 during aging seems to be required in order to reinforce the NL [17]. Last decade, the studies from Frost and collaborators in a *Drosophila melanogaster* model of AD demonstrated that NL plays a decisive role at the starting point of the disease [18], defining AD as an acquired laminopathy [19]. Recently, altered conformations of NL associated to aging as well as to Alzheimer´s pathology have been reported in hippocampal neurons [17]. Human postmitotic neurons usually display a characteristic absence of Lamin A at their NL, and a unique and large nucleolus which congregates most of the nucleolus organizing regions (NORs) [20,21]. The absence of Lamin A confers greater flexibility to the nucleoskeleton, favoring the fluid interaction between the cytoskeleton and the nucleus required for neuronal plasticity [22–24].

Interestingly, Lamin A is involved both in physiological aging and in an accelerated aging process leading to very premature death, namely Hutchinson-Gilford syndrome (HGPS). A dysfunctional NL of fibroblasts and the subsequent DNA damage underlie HGPS. Therefore, it is considered a genetic laminopathy. The affected children present connective tissue alterations, which result in pathologies that would generally occur in advanced biological age in several organs such as bone, muscle, skin, blood vessels, and subcutaneous tissues. Nevertheless, not all organs are affected, the brain is spared given the absence of Lamin A in postmitotic neurons and does not present characteristic signs of neurodegeneration associated with advanced age such as AD [25].

Sporadic AD is a multifactorial disease whose etiology remains unknown, but where the main risk factor is aging [6]. Old neurons display a more complex and less flexible NL than young neurons but still with a certain degree of plasticity, allowing mechanical interaction between the aged nucleus and cytoplasm [22,23,14]. Recently, it has been demonstrated that in aged AD brains, postmitotic hippocampal cells express Lamin A from the initial stages of the disease [16]. The NL structure of AD neurons is even more complex than in healthy aged neurons, since it expresses at least 3 intermediate filaments type V, Lamin B1, B2, and also Lamin A [17]. The presence of Lamin A fortifies the NL, providing greater rigidity and viscosity that prevents nuclear deformation [14]. These findings suggest that a dysfunctional NL is implicated in both aging and AD [19], whereby the up regulation of Lamin A expression is one of the most significant differences between healthy senile and AD brains [16].

2.2. Lamin A and neuronal aging

An exciting relationship between Lamin A, HGPS and normal aging has been recently demonstrated. In prematurely aged fibroblasts from HGPS patients, NL dysfunction is due to a dominant punctual mutation in the LMNA gene (1874C-T). This change generates a truncated Lamin A lacking 50 aminoacids in its C-terminus, which is permanently farnesylated (Lamin A50/progerin) [26–28]. Lamin A50 becomes abnormally associated with the membrane and organizes a dysfunctional pseudo-structure of type V filaments that accumulates in the nuclear periphery [29,30]. The resultant defective NL does not provide the adequate restrain deformation rate and strength required by the cell nucleus to anchor and stabilize peripheral and nucleoplasmic heterochromatin [31]. Instead, it forms a weak and viscous interaction with heterochromatin [32,33], which lacks the mechanical dynamics with the robust cytoskeleton resulting in pathologic alterations of the nucleus and chromatin [14].

Normal aging is also associated to the presence of Lamin A50, through alternative splicing of the LMNA gene. This has been established by demonstrating the presence of mRNA of Lamin A50 in fibroblasts from young and old subjects [34]. Although the expression of Lamin A50 was 50 times higher in HGPS cells as compared with the healthy fibroblasts, this study indicates that healthy cells also contain Lamin A50 at much lower levels than HGSP cells. Cells from old subjects show 2 striking differences from those from young ones. First, they express low levels of Lamin A50, and second, while cells from young subjects express it throughout the nucleoplasm, these cells express Lamin A only at the rim of the nuclear membrane, which is a similar distribution of mutant lamin in HGSP cells. Importantly, this aberrant splicing event driving to a lack of nucleoplasmic Lamin A is associated with substantial changes in epigenetic markers and an increased amount of unrepaired DNA damage [34]. All this suggests that the truncated Lamin A isoform is physiologically related to aging, although its function is still unknown.

Lamin A is not present in the neuronal NL and is not implicated in their aging process either. Nevertheless, its expression plays a key role in the transformation from senile to AD neurons [16]. Besides, its position at the nuclear periphery is similar to that observed in HGPS fibroblasts, suggesting a non-canonical function. Early AD stages are characterized by radical structural and regulatory changes of the nucleus of hippocampal pyramidal neurons (Fig. 1). These changes progressively lead to cytoskeleton dysfunction, which can be observed years later in the form of neurofibrillary tangles [35]. Concerning the nuclear periphery, Lamin A appearance at the internal side of the aged NL generates an increased rigidity of the nuclear scaffold, mechanical changes of cytoskeleton-nuclear transduction and a different chromatin viscosity [14]. Future research will determine whether AD neurons express only normal length Lamin A or also the truncated Lamin A related to physiological aging.

3. Nuclear Tau: chromatin modifier in aging and Alzheimer´s disease

Chromatin structure safeguards the integrity and expression of the genome. Its dynamics rule the temporal-cellular implementation of specific genetic programs that regulate the development and age-related changes of biological functions in cells and tissues [2]. Aging and progressive chromatin deterioration is associated with increased DNA damage in all tissues [36–39]. The main processes accounting for DNA damage both in proliferative and postmitotic aging cells [40] are the accumulation of unrepairable double-strand breaks [41,42], genome rearrangements [43] and the decrement of repair capacity with age [44,45].

3.1. Nuclear Tau and chromatin aging

Tau protein stands out among the proteins with an essential diversity of neuronal functions. In the cytoskeleton is a microtubule-associated protein, which stabilizes microtubules and promotes their assembly. Its phosphorylation is associated with a detachment from microtubules and is essential for neuronal plasticity in the healthy brain. Nevertheless, hyperphosphorylation drives Tau aggregation and the production of neurofibrillary tangles in pathological aging and tauopathies [35]. More recently, its nuclear presence and DNA binding have been widely demonstrated [46–50] as well as its protective role against oxidative and heat stress, which is related to Tau concentration [46,51,52].

Strand breaks caused by endogenous reactive oxygen species (ROS) are among the main causes of DNA damage. The high oxygen consumption rate of postmitotic neurons leads to a progressive accumulation of oxidized DNA during decades of brain aging, which is especially remarkable in AD brains [53,54]. In this context, the amount of one form of phosphorylated Tau, AT100 (p-The212-Ser214) in hippocampal CA1 and dentate gyrus (DG) neurons increases with age, reaching its higher levels in the oldest neurons and those subjected to oxidative stress [55,56]. Young neuronal nuclei display scarce, and weak AT100 positivity in a disperse punctuate pattern. As neurons age, the positivity zones increase in frequency and intensity, in particular close to the nu-

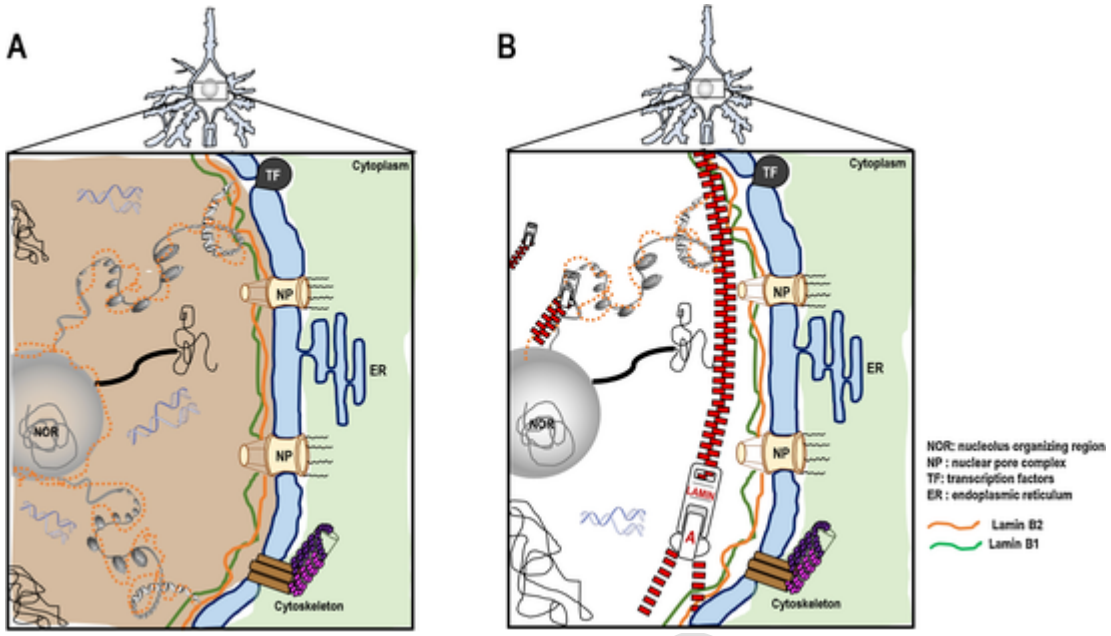

Fig. 1. Transformation from senile to AD pyramidal neurons. (A) Lamin A is not present in the neuronal nuclear lamina, the senile neurons display an increment of Lamin B2 in their NL, with redistribution to replication factories where it reinforces the LADs. (B) The addition of Lamin A to Lamin B1 and B2 will increase the stiffness of the nuclear lamina, resulting in a limited nuclear deformation and reduced chromatin mobility. Hence, the spatial chromatin organization, gene expression regulation, and nucleus-cytoplasm transport are modified in the AD neuron.

clear membrane and around the nucleolus, colocalizing with the rich DAPI stained heterochromatin regions [49,57,58]. The most significant finding is the vast presence of AT100 in the nuclei of old neurons interacting both with heterochromatin and euchromatin in the nuclear periphery and the nucleolus [56]. This progressive up-regulation of Tau in parallel with age–related DNA damage due to oxidation and rupture would confirm its participation, ensuring genome stability and function throughout healthy neuronal aging [59,43].

In addition to DNA strand breaks, the electron microscopy analysis of 30 nm chromatin fibers in aging fibroblasts shows a progressive loss of density [60,61], which indicates a decrease of chromatin compaction along with lifespan [62]. Heterochromatin regions like telomeres, pericentromeres, and those coding for ribosomal proteins undergo the most drastic changes with age [63–65]. One of the main causes of chromatin decompaction is the loss of histone proteins, which reaches a 50% diminution of the histone core [2,66,67]. Interestingly, Tau binds the minor groove of DNA forming a beads-on-a-string structure similar to histone binding [67]. Tau is predominantly present at the border of the nucleolus, where it colocalizes with H3K9me2, an epigenetic mark of constitutive heterochromatin [48]. Throughout neuronal aging chromatin fibers would loss nucleosomes, but their interaction with nuclear Tau increases in order to keep a functional compaction level. This behavior supports the hypothesis that Tau plays a protective role in stress situations such as physiological aging [55].

3.2. Nuclear Tau and global chromatin decondensation in AD neurons

Age-related chromatin changes increase the incidence of age-related diseases like AD. Postmortem histological analysis of hippocampal cells at early AD stages, previous to the presence of NFTs, reveals the presence of two characteristics that distinguish them from healthy senile brains. First, the anomalous presence of Lamin A described in the previous section, and second, the gradual appearance of Tau in the cytoplasm [68,69]. The nuclei of senile neurons from the CA1 and DG regions show high AT100 immunopositivity. The aged and damaged chromatin is thought to be protected and stabilized by this phosphorylated form of Tau [56]. At early AD stages, however, depletion of nuclear Tau advances gradually as AD progresses, and it reaches its maximum at late AD stages when AT100 immunopositivity is exclusively localized in neurofibrillary tangles (NFTs); and the nuclei are completely devoid of Tau [70]. Tau exit from neuronal nuclei induces global chromatin relaxation, namely extended fibers and fibers without nucleosomes [18]. This relaxed chromatin presents 1) important epigenetic changes [71], 2) dysregulation of euchromatin genes and 3) abnormal transcription of heterochromatin genes [18,57,72,73] and of transposable elements [74]. All these characteristics support a role of nuclear Tau in chromatin protection.

The decrease of marks associated to transcriptional silencing such as H3K9me2/me3 downstream nuclear Tau depletion [18,70] leads to constitutive heterochromatin decondensation at the pericentromeric and perinuclear regions called LADs (lamin associated domains) due to their close relationship with NL [56,57,75] and with nucleolar regions denominated NADs [48,58,50]. This decondensation is the consequence of a synchronized overall increase of activating epigenetic marks such the histones acetylations H4K16ac, H3K12ac and H3K9ac [17,70,71,76,77].

Tau is localized adjacent to the inner side of the NL [56,75] and regulates the nuclear pore complex (NPC). The progressive accumulation of Tau in the somatodendritic compartment along AD stages affects the structure of NL and disrupts nucleocytoplasm transport and results in the mislocalization of nuclear proteins in the cytoplasm [78]. The critical role of Tau on the structural and functional regulation of the genome has been revealed employing genoma-wide immunoprecipitation (ChiP) and microarray hybridation (ChiP-on-chip) assays [79]. Non-protein coding DNA sequences are targets of nuclear Tau, which binds to GAGA motifs distributed throughout the genome. The presence of GAGA repeats in the LADs associated to NL [80] confirms Tau participation in the organization of perinuclear heterochromatin. Therefore, the exit of Tau from the neuronal AD nuclei implies the destabilization of chromatin domains and the remodeling of LADs [18,56].

Significant amounts of Tau protein interact with DNA intergenic and intronic regions coding for long noncoding RNA (lncRNA), which are chromatin regulators [79,81]. These lncRNA act as molecular scaffolds through direct or indirect association with chromatin-modifying

factors such as methyl and acetyltransferases, deacetylases and kinases [82–84]. Also, through their interaction with transcription factors, Tau and lncRNAs regulate the transcription state of chromatin and, indirectly, the expression of genes involved in cellular processes that are highly dysregulated during aging [2,67,85–87] and in AD [88–90]. Recent evidences point to the role of lncRNAs in AD [91,92].

Nucleolar dysfunction in AD has been widely documented [70,93,94]. Tau is present in the nucleolus, both in the euchromatic regions harboring ribosomal genes (rDNA) and in the NADs [17,48,50,56,95,96]. Nucleolar Tau depletion has been reported to affect rRNA synthesis and to destabilize rDNA loci [58]. In the hippocampus, Tau depletion decreases the ratio of mature rRNA 28 s and deregulates the expression of proteins involved in translation [70]. Altogether, nucleolar Tau presence is essential for NADs stability, rDNA transcriptional regulation, and the structure and function of the nucleolus.

In summary, Tau is a key player in the healthy aging of postmitotic hippocampal neurons. Its nuclear expression along decades protects genomic DNA and stabilizes the peripheral (LADs) and nucleolar (NADs) heterochromatin blocks [57,58,97], by allowing the required chromatin compaction in order to silence the repetitive DNA sequences and to warrant hippocampal gene regulation. Still, it has not been elucidated the precise stimuli that trigger Tau exit from the nucleus and the cascade of events leading to the dysfunctional AD neuron, whose characteristics are documented in detail as follows, 1) decondensed global chromatin [18]; 2) activation of previously silenced intergenic and non-coding sequences in heterochromatin regions [57,74,79,91,92,98]; 3) repression of characteristic postmitotic neuron genes and expression of new genes [71,79,88,90]; 4) dysfunctional transcription and translation [70,99]; 5) disorganized NL and nucleoskeleton resulting in abnormal nucleus-cytoplasmic transport [17,75]. The final consequence of these long-standing changes will be the main characteristics of AD, namely loss of neuronal plasticity and the presence of NFTs.

4. Lamin A rescues neurons from death following aberrant cell cycle reentry in AD

Neuronal aging underlies the neurodegeneration observed under sporadic AD. Terminally differentiated neurons are highly susceptible to oxidative DNA damage due to their high rate of oxidative metabolism [100]. High levels of damaged DNA have been detected at autopsy of hippocampal tissue both from healthy senile subjects and from AD patients [101]. Neuronal DNA damage at senile stages is markedly localized at the promoter regions of genes involved in learning, memory and neuronal survival, which already show a reduced expression after the age of 40 years [102]. In parallel, a reduction of markers of DNA repair [102,103] implicates a mismatch between patterns of damage and successful repair. Unrepaired or incorrectly repaired double-strand breaks are the most lethal damage that can occur to DNA.

4.1. Neuronal aging and cell cycle reentry

Reliable evidence indicates that the failure to repair DNA damage is the determinant factor leading to the activation of an aberrant cell cycle [104]. Aged neurons arriving at a particular "vulnerability" point require to express repairing proteins by activating the S checkpoint. In addition to AD, this phenomenon has been described in other neurodegenerative diseases such as Parkinson´s disease and amyotrophic lateral sclerosis as well as in retinal degenerative disorders [105]. In fact, the activation of DNA repair pathways has been demonstrated following the G0-G1 transition of postmitotic neurons [106,107]. Even in absence of AD markers, the expression of cyclin E has been reported in elderly CA1 neurons [108]. Also, in the entorhinal cortex up to 10% of hyperploid pyramidal neurons have been quantified [109]. When cell cycle reentry is forced in cortical cultures, it has been demonstrated that although hyperploid neurons remain connected to normal diploid cells and seem to maintain their basic electrophysiological properties, excitability and spontaneous activity show an important decrease [110].

The study of cell cycle reentry in cultures of primary cortical neurons and animal models has revealed that it requires the presence of soluble Tau and beta amyloid (Aβ) before they become incorporated into tangles and plaques, respectively [18,111–114]. Aβ has antioxidant properties [115,116]. Oxidative stress activates positive feedback between gamma and beta-secretase cleavage of beta-amyloid precursor protein (APP) and increases the expression and activity of beta-secretase [117,118]. On the other hand, nuclear Tau has a concentration-dependent protective role of DNA oxidation [46,51,52]. Throughout healthy neuronal aging, an up-regulation of nuclear Tau becomes evident through the progressive accumulation phosphorylated Tau in the site Thr212-Ser214 (AT100). The nucleus of senile neurons entering cell-cycle displays the highest presence of AT100 accompanied by a reorganization of NL, whereby Lamin B2 is redistributed from the nuclear envelops to the nucleoplasm [56,17]. Lamin B2 redistribution to replication factories takes place during the S phase [119], indicating a direct role in DNA synthesis [120] and the conversion of hyperploid neurons [109,121].

Once the genome has been replicated, the neurons continue to the G2-M phase, from which they are unable to progress [122]. Interestingly, although these hyperploid neurons present synaptic dysfunction, they continue integrated in networks with diploid neurons, which favors their survival. It has been hypothesized that these dysfunctional networks could be underlying the cognitive deficits found in AD [123]. Finally, hyperploid neurons end in cell death [108,124,125]. It is a fact that healthy aging involves neuronal loss, and aberrant cell-cycle reentry seems to provoke between 5 and 10% of hippocampal neuronal death [122]. It is also plausible that this neuronal loss slowly starts as soon as after age 40 when a reduced expression of genes responsible for neuronal survival and plasticity decreases [102]. Multiple *in vitro* studies employing cell cultures and *in vivo* research in murine AD models confirm that neuronal death is a consequence of cell cycle reentry [126–130]. A sustained neuronal loss takes place along 2–3 decades of healthy aging without a significant impact on cognitive skills [131].

4.2. Lamin A and nuclear Tau: crucial players blocking the consequences of cell cycle reentry

Notwithstanding this deadly pathway for aging neurons, why and how senile neurons that enter the aberrant cell cycle that leads them to death, transform themselves in dysfunctional AD neurons, which are able to survive through several years? We do not have a complete answer yet. For almost 30 years, it is known that two groups of neurons coexist in AD brains at initial stages. One of them suffers the abortive cell cycle and accounts for 75–90% of the neuronal loss by the time the disease progresses to later AD stages [128,132,133], while the second type of neurons do not die but triggers Tau hyperphosphorylation and aggregation, originating NFTs. These neurons suffer from a nucleo-cytoskeleton disruption, and even the extracellular matrix becomes invaded by protein aggregates, but these changes enable them to survive for years [108,134,135]. As commented above, the involvement of nuclear Tau at the beginning of AD has been demonstrated [70]. It is important to underline, however, that new nuclear Tau phosphorylation takes place in senile neurons, in addition to the AT100 site. The phosphorylation of the emblematic site Ser202-Thr205 (AT8) results in a paper clip conformation [136], which is the pathological structure characteristic for Tau in AD. Tau is an unfolded protein whose phosphorylation determines its structure and function [137]. The phosphorylated AT8 site is related to inhibition of replication [138], inactiva-

tion of rDNA transcription [96], and preservation of vulnerable neurons in G0 [108]. This clearly indicates a key role of nuclear Tau by blocking the cell cycle while keeping the vulnerable neurons in a viable, static G0-G1 in the aged hippocampus [17]. The phosphorylation of residues T205-T212-S214 of the proline-rich domain [136] are the characteristic of nuclear and cytoplasmic Tau forms during aging and neurodegeneration [139,140,136]. The structural change associated to phosphorylation of the same or different nuclear Tau isoforms [141,142] is involved not only in neuronal differentiation but also in cellular stress [96,143]. Altogether, these versatile functions of nuclear Tau suggest that it protects heterochromatin stability and is able to modify DNA expression [144].

The senile and vulnerable neurons that had enriched their nuclei with hyperphosphorylated Tau also display an increment of Lamin B2 in their NL, where it reinforces the LADs and immobilizes the shortened telomeres associated to the aging process [145]. However, senile neurons that migrate to the AD phenotype suffer an irreversible nuclear transformation that affects not only the neuron itself but complete circuits, and finally, the whole brain, although the details of its propagation are still under study [146]. Tau exit from the nucleus has pathogenic effects that decisively contribute to synaptic dysfunction and neurodegeneration [70]. The first effect is associated with Tau accumulation in the somatodendritic compartment that directly impairs RNA translation [147,148] and inversely correlates with translational output [149,150]. Besides, it drives the transformation of the nucleoskeleton of the AD neuron towards chromatin relaxation, preferentially observed in the LADs and H3K9ac associated domains [71]. As mentioned in the previous section, the spatial chromatin organization, the silencing of heterochromatin blocks, gene expression regulation, and nucleus-cytoplasm transport are modified in the AD neuron (Fig. 2). The decondensation of repetitive DNA sequences implies, among other effects, the disinhibition of brain-specific miR-9 [19], which enables the anomalous expression of Lamin A in more than 50% hippocampal neurons [16,17], influencing at least 2 ongoing processes. First, it arrests DNA replication, which prolongs neuronal life by keeping them in an artificial G1 phase of the initiated cell cycle [151]. Second, it decreases DNA damage through the activation of DNA repair mechanisms such as DNA double-strand break repair (DSB) and DNA excision repair (BER) [152–154]. Despite the genomic stability conferred by Lamin A expression, the excessive ectopic expression of extranuclear kinases will contribute to hyperphosphorylate Tau [122,155]. Similarly, as it takes place in HGPS [156], the perinuclear Lamin A accumulation in AD will be associated to an increased expression of the repressive histone mark H4K20me3 during early and intermediate AD Braak stages [17]. The labile heterochromatin blocks at NADs and LADs will be stabilized through H4K20me3 [57,71,157–159], since they are devoid of nuclear Tau and histone 3 at this stage [70,160].

Pyramidal hippocampal neurons do not express Lamin A, which allows the required nuclear flexibility to deploy their high degree of axonal and dendritic plasticity [23]. The addition of Lamin A to the dimeric network conformed by Lamin B1 and B2 will increase the NL stiffness, resulting in a limited nuclear deformation and reduced chromatin mobility [14,23]. The dynamics of the nucleus-cytoplasm scaffold suffers a decisive modification, since Lamin A regulates the expression of cytoplasmic stress fibers, nuclear actin, and myosin I [23]. This cytoplasmic transformation would finally lead to the production of NFT by cytoplasmic hyperphosphorylated Tau and a disorganized mass of microtubule subunits [161].

It is worth finally mentioning here that the expression of cell cycle markers is not exclusive of AD but has also been reported in other neurodegenerative diseases such as Parkinson [162] amyotrophic lateral sclerosis [163] and Huntington´s disease [164] as well as in stressful situations such as stroke [165] and viral encephalitis [166]. Similarly, "mitotic catastrophes" have also been reported in other postmitotic cells such as podocytes [167], cardiomyocytes [168], muscle fibers [169], and retinal pigmental epithelial cells [170].

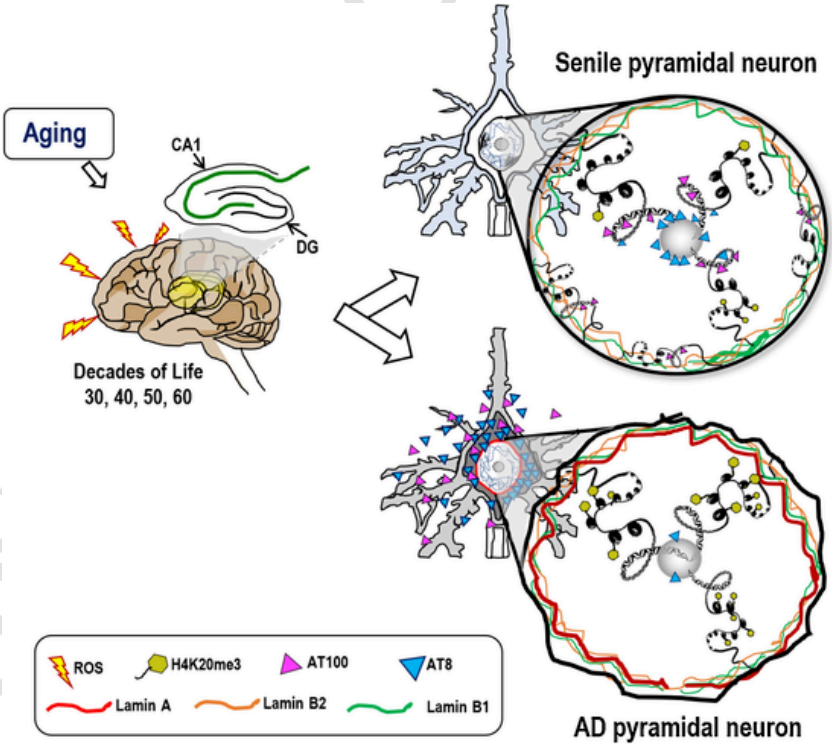

Fig. 2. Nuclear Tau and neuronal AD transformation. Postmitotic neurons accumulate DNA damage during decades of brain aging. Nuclear Tau expression protects genomic DNA and stabilizes the peripheral and nucleolar heterochromatin blocks in the senile neuron. The phosphorylated AT100 and AT8 sites block the cell cycle while keeping the vulnerable neurons quiescent in the aged hippocampus. After Tau exit from the AD nucleus, the extracellular matrix becomes invaded by protein aggregates, although these changes enable them to survive some years despite synaptic dysfunction.

5. Conclusion

It is very plausible that cell cycle reentry has evolved as a biological mechanism associated with stress in order to restore the nuclear-cellular-tissue homeostasis. Aging may represent an extreme stress situation whereby cell cycle reentry does not allow to recover the equilibrium, resulting in a cascade of finally pathologic events. In the case of replicative cells, cancer may be the outcome, while in the case of postmitotic cells, degeneration and death would be the consequence.

This latter scenario is evidenced in pyramidal hippocampal neurons, whose cell cycle reentry throughout aging is the main cause of neuronal loss. These cells are temporarily rescued from death through the anomalous Lamin A expression and Tau exit from the neuronal nuclei forming NFTs. Nevertheless, research is needed in order to elucidate whether Lamin A expression also triggers a mechanotransduction dysfunction [171], leading hippocampal neurons to neurodegeneration.

Declaration of Competing Interest

The authors declare no conflict of interest.

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