Chapter 7

Human nuclear tau and aging

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List of abbreviations

AD Alzheimer disease
AT100 Tau epitope with phosphorylated Thr212/Ser214 residues
CA1 Cornus ammonis 1
CNS central nervous system
DFC dense fibrillar component (of the nucleolus)
DG dentate gyrus
HiC high-throughput chromosome capture
MAPT microtubule-associated protein tau gene
MTBD microtubule-binding domain in tau protein
NFT neurofibrillary tangles
NOR nucleolar organizing regions
PNS peripheral nervous system
PRD proline-rich domain in tau protein
rDNA ribosomal gene cluster
TAD topologically associated domain
Tau-1 Tau epitope with nonphosphorylated Pro189/Gly207 residues
UBTF upstream binding transcription factor

Mini-dictionary of terms

Cornus ammonis 1: subfield of the more extended hippocampal region containing densely packed pyramidal cells.
Dentate Gyrus: hippocampal region made by a layer of granule neurons.
HiC: method used to study the interactions between loci in a genome-wide approach.
Human α-satellite: centromeric sequences made of highly repetitive sequences.
Neurofibrillary tangles: intracellular insoluble aggregations of hyperphosphorylated tau protein.
Neurodegeneration: molecular events that progressively lead to neuron's loss of structure and function.
SH3 domains: sequences of about 60 amino acid residues involved in cellular signaling and regulating pathways.
TADs: genomic regions endowed by a loop organization, with high levels of self-interactions with respect to interactions among different TADs.
Taupathies: group of degenerative disorders endowed by the accumulation of abnormal tau protein within the cells.

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Factors Affecting Neurological Aging. https://doi.org/10.1016/B978-0-12-817990-1.00007-X
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Introduction

Tau belongs to the Microtubule-Associated Proteins (MAPs), a family of proteins involved in cytoskeletal dynamics. Its structure is composed of four domains, and since its first identification (Weingarten, Lockwood, Hwo, & Kirschner, 1975), its role in microtubule organization and neuronal axonal transport has been demonstrated. The *microtubule-associated protein tau* (*MAPT*) gene encodes a pre-mRNA that, by alternative splicing, produces different mature transcripts, and codifies several protein variants, differentially expressed during neuronal development. In the human brain, six main isoforms were found, related to the alternative splicing of exons 2, 3, and 10 (Andreadis, 2005).

Moreover, tau can be post-translationally modified at a number of sites, thus increasing the complexity of its regulation. These modifications, phosphorylation being the most relevant, regulate tau functions, and abnormal modifications, such as hyperphosphorylations, characterize a group of disorders called "taupathies". The accumulation of intracellular filamentous deposits, due to hyperphosphorylation and an aggregation of tau, occurs in Alzheimer disease (AD), frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17), amyotrophic lateral sclerosis (ALS), cortical basal degeneration, and other neurodegenerative diseases (Alonso et al., 2018; Naseri, Wang, Guo, Sharma, & Luo, 2019).

Tau protein was first identified as a cytoplasmic protein. Later studies demonstrated its presence in the nucleus and that it can bind dsDNA in the minor groove (Qi et al., 2015), but the exact role of nuclear tau is still little known. The different isoforms of nuclear tau show various expression patterns in replicative or differentiated cells, and specific epitopes observed in the nucleus, both in neurons and other cell types, are the phosphorylated AT8 (pSer202/Thr205), AT100 (pThr212/Ser214), and the unphosphorylated Tau-1 (Pro189/Gly207) (Federico et al., 2018; Gil et al., 2017). The main nuclear location of these tau epitopes is the nucleolus, endowed with important functions for cellular homeostasis, and characterized by morphological changes along the cell cycle, depending on interactions with a number of molecules. The nucleolus is a dynamic structure that modifies its organization during cell proliferation and differentiation, with alterations related to cell aging, and often to a number of diseases involving cell alterations, such as in cancers or degenerative disorders. Moreover, nuclear tau seems to play an important role in nucleolar physiology and dysfunction.

The *MAPT* gene

Genomic structure and expression

The human *MAPT* gene spans 134 Kb of the genome in the chromosomal band 17q21.31. It is transcribed in three different transcripts with sizes of 2, 6, and 8/9 Kb, expressed in the nervous system depending on the neuron type and on the neuronal maturation stage. Tau protein codified by the 2 Kb transcript has been mainly observed in the cell nucleus, with that codified by the 6 Kb transcript detected in the brain neurons, and by the 8/9 Kb in the retina and in the Peripheral Nervous System (PNS) (Andreadis, 2005). The *MAPT* gene is composed of 16 exons, some of them alternatively spliced generating different isoforms of tau. The nuclear tau is codified by the smaller transcript composed of the constitutively expressed exons 1, 4, 5, 7, 9, 11, 12, and 13 and by the alternatively spliced exons 2, 3, and 10 (Fig. 7.1), resulting in six different isoforms of tau. Their sizes range from 352 to 441 amino acids, with a molecular weight (MW) between 60 and 74 kDa, and they are differentially expressed during the postnatal development of the human brain (Fig. 7.2).

The six isoforms are called 2N3R, 1N3R, 0N3R, 2N4R, 1N4R, and 0N4R depending on absence/presence of exons 2/3 (0N/1N/2N), and the absence/presence of exon 10 (3R/4R) (Bukar Maina, Al-Hilaly, & Serpell, 2016). The smaller isoform (0N3R) is only found in the fetal brain, and transitorily during neurogenesis. It contains three microtubule binding repeats (3R) at the C-terminal, and no insert repeats (0N) at the N-terminal of the protein. Instead, the larger isoforms are mainly present in the adult brain.

Pathological mutations

Many pathological mutations have been described in the human *MAPT* gene, with large numbers of them mainly located in exons 9 to 13, including missense and silent mutations as well as deletions. These mutations often influence the assembly and binding of tau with the microtubules, determining a reduction in stability, and increasing the level of free tau in the cytoplasm of the neurons. This may allow the pathological aggregation and subsequent formation of the NFTs (neurofibrillary tangles) found in the brain of patients with AD. On the contrary, there are also mutations that increase tau's ability to promote microtubule assembly. Other mutations, with the potential to induce taupathies, are located in the introns. The intronic, and some exonic, mutations interfere with the splicing of exon 10, thus altering the ratio between the 3R and 4R isoforms. This occurs due to the alteration of the secondary structure of the RNA in the splicing site, which determines the inclusion of exon 10 in the mature mRNA. This leads to an increase in the amount of transcripts codifying

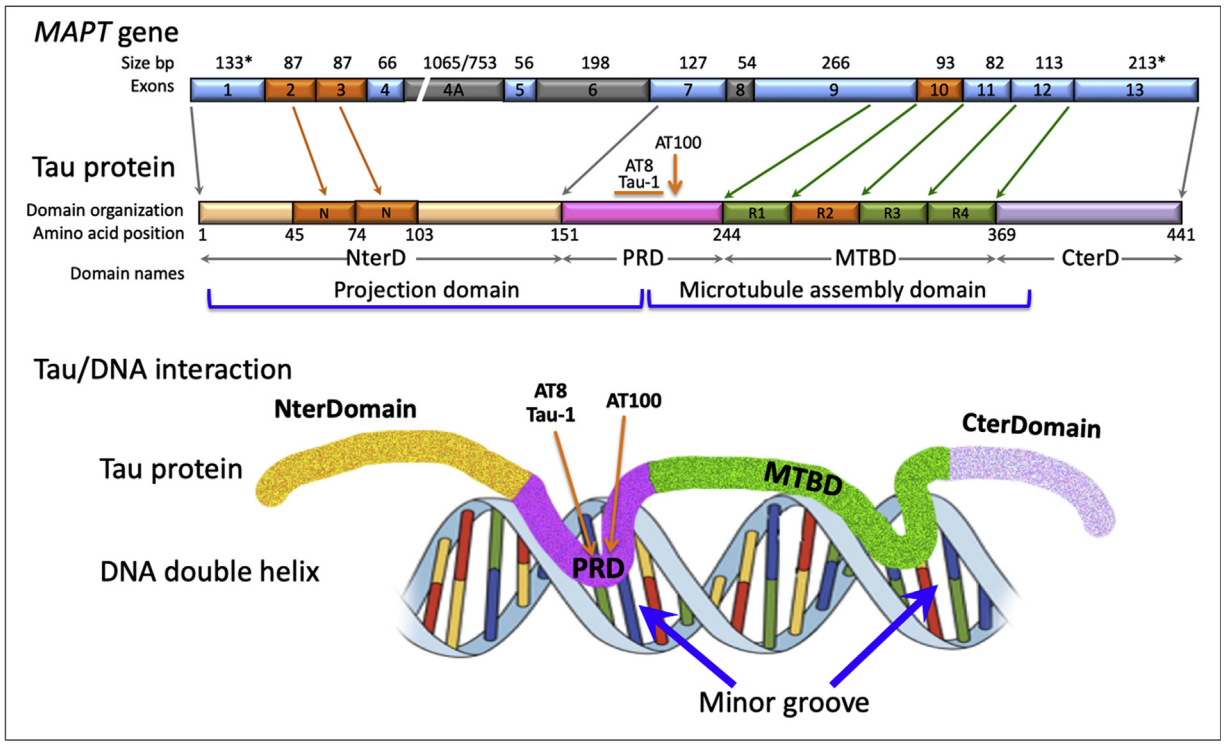

FIGURE 7.1 *MAPT* gene and tau protein. *Upper*: exons of the *MAPT* gene between start and stop codons. Pale blue, orange, and gray exons are constitutively, alternatively spliced, or not included, respectively, in the nuclear tau mRNA. *Middle*: Tau protein domains. The position of Tau-1, AT8, and AT100 epitopes are indicated. *CterD*, C-terminal domain; *MTDB*, microtubule-binding domain; *NterD*, N-terminal domain; *PRD*, proline-rich domain. *Bottom*: schematic representation of the possible interaction between the tau protein and the DNA double helix.

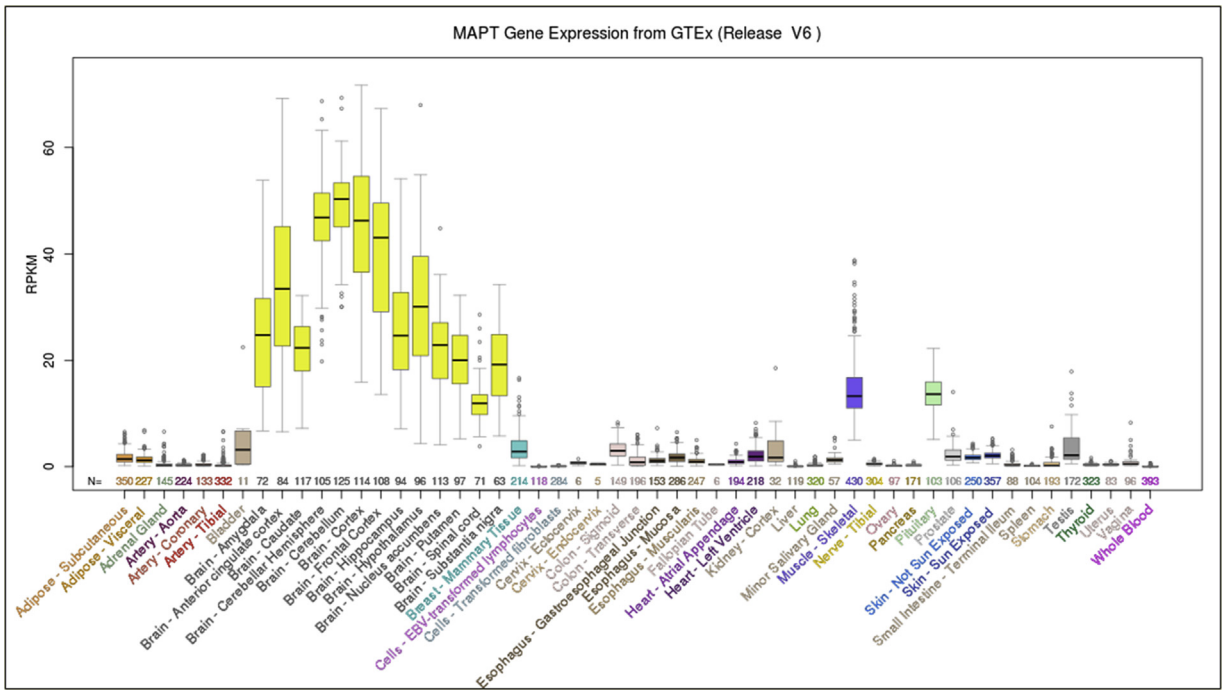

FIGURE 7.2 *MAPT* gene expression. Expression level of the *MAPT* gene from GTEx-V6 (Genotype-Tissue Expression, Release V6). Note the high level of expression in neuronal cells. *Data from* http://ucsc.genome.edu.

the 4R isoform (McCarty et al., 2015; Park, Ahn, & Gallo, 2016). It is unclear what mechanisms lie at the basis of the neurodegeneration due to the altered ratio among the 3R and 4R isoforms, but it is generally accepted that isoform-dependent aggregations of tau became pathological when the 3R/4R ratio is altered.

Tau protein

Tau organization and functional domains

Tau (tubulin associated unit) is a protein with a low molecular weight, is unusually hydrophilic, and thus is highly soluble and stable in different conditions, such as acidity and heat. Tau was defined as "natively unfolded," with a number of biophysical properties described that could allow interactions not only with a variety of other cell proteins, but also between domains of the same tau protein. These interactions often resemble a "paper clip," with the N-terminal and C-terminal joined together (Guo, Noble, & Hanger, 2017). Indeed, tau is composed of four main domains: the N-terminal domain, followed by the proline-rich domain (PRD), then the microtubule binding domain (MTBD), and the C-terminal domain (Fig. 7.1).

The N-terminal of tau is defined as "projection domain" because it protrudes from the microtubule surface, when tau is anchored on them, to interact with other cytoskeleton elements and with the plasma membrane of the neurons. This allows it to maintain a specific distance from the microtubules and to regulate the axonal diameter. The *projection domain* can be divided into two domains: one proximal, rich in acidic residues, and the other distal, rich in prolines (PRD). The acidic-rich domain is codified by the alternatively spliced exons 2/3 and presents the two sequences of 29 amino acidic residues differently used in the 0N, 1N, 2N isoforms, and thus interacts with other proteins in an isoform-specific way. The PRD contains the SerPro or ThrPro motifs, which are targets of the proline-directed kinases, and seven Pro-X-X-Pro motifs, which are binding sites of proteins with SH3 domains. The abnormal binding of these latter proteins with tau interferes with microtubule stability and may produce alterations in neuronal plasticity (Mufson et al., 2015; Zabik, Imhof, & Martic-Milne, 2017).

Tau's ability to bind microtubules is mediated by MTBD, composed of four repeats (R1 to R4) codified by exons 9 to 12, respectively. Each repeat is composed of 31/32 amino acids, and can be subdivided into two parts: one containing 18 highly conserved amino acids, representing the minimal region required to bind tubulin, and the other composed of 13/14 amino acids, which are less conserved, and act as separators (inter-repeat) of the microtubule binding part. The first two repeats, and the inter-repeat between them, define the main core of the MTBD (Goode, Chau, Denis, & Feinstein, 2000). Considering that the second repeat is codified by the alternatively spliced exon 10, the 3R and 4R isoforms have been described to show differing efficiencies to bind microtubules. Indeed, the 4R isoforms more efficiently promote the microtubule assembly in respect to 3R, and this higher affinity for microtubules resides in the peptide KVQIINKK, located at the 274−281 position in the 4R isoform (Tapia-Rojas et al., 2019).

Post-translational modifications: phosphorylation

Phosphorylation is the most studied post-translational modification of tau and probably the most important, considering its role in controlling the affinity for microtubules, and in defining the specific intracellular position. The longest isoform of tau described in the human brain, the 2N4R, has 85 potential sites of phosphorylation: 45 serines, 35 threonines, and 5 tyrosines. Among them, 31 sites have been associated with physiological functions, and another 16 were detected in pathological conditions (Martin, Latypova, & Terro, 2011).

The large numbers of phosphorylatable sites are located outside the MTBD, except Ser262 (in the R1 repeat of the MTBD), Ser293 (in the R2 repeat), Ser305 (between the R2 and R3 domains), Ser324 (in the R3 domain), Ser352, and Ser356 (in the R4 domain). Phosphorylations in Ser262, Ser293, Ser324, and Ser356, located in the motif KXGS of the R1, R2, R3, R4, respectively, reduce the binding affinity of tau to microtubules. Ser262 drastically reduces tau affinity to microtubules in vitro, but this phosphorylated site is not enough to block microtubule binding, and phosphorylation in Thr231 and Ser235, in the PRD, negatively influence binding to the microtubules (Sergeant et al., 2008). Thus, phosphorylated sites in the N-terminal PRD reduce tau's ability to promote microtubule nucleation, indicating that regions outside the MTBD can also influence tau associations with microtubules (Mi & Johnson, 2006; Shahani & Brandt, 2002). Two phosphorylated sites in the PRD region seem to be relevant in the interaction with DNA. These are AT8 and AT100 epitopes, corresponding to pSer202/Thr205 and pThr212/Ser214, respectively.

Nuclear location of the tau protein

The presence of tau protein in the nucleus of neurons was first demonstrated in 1988 in patients with AD, and in human neuroblastoma cells (Loomis, Howard, Castleberry, & Binder, 1990; Metuzals, Robitaille, Houghton, Gauthier, &

Leblanc, 1988). Tau was detected in the Nucleolar Organizing Regions (NORs) of the acrocentric chromosomes, and in the fibrillary region of the nucleolus of neuronal and nonneuronal cells, such as lymphocytes and fibroblasts (Federico et al., 2018; Thurston, Zinkowski, & Binder, 1996). In this compartment, tau may bind DNA, and it was shown that tau dysfunction following phosphorylations, such as in AD, can induce disaggregation from DNA (Hua et al., 2003).

Tau can bind and fold DNA (Fig. 7.1), in the minor groove, via PRD and MTBD regions, at the level of the second part of the PRD, and of the R2 repeat in MTBD (Krylova et al., 2005; Wei et al., 2008). This binding seems to be independent of the nucleotide sequence, even though a specific binding with the human α-satellite was also described (Sjöberg, Shestakova, Mansuroglu, Maccioni, & Bonnefoy, 2006).

Recently, the shorter isoform of tau 0N3R was detected in neuroblastoma cells during neuronal differentiation, and specifically the epitopes Tau-1 and AT8, detecting the unphosphorylated and the phosphorylated Ser202/Thr205 region, respectively. AT8 is undetected in replicative neuroblastoma cells, and appears during neuronal cell differentiation (Fig. 7.3); instead, the unphosphorylated Tau-1 epitope was observed in both replicative and differentiated cells, in a spot-like distribution colocalizing with the Upstream Binding Transcription Factor (UBTF) (Fig. 7.4). Moreover, another

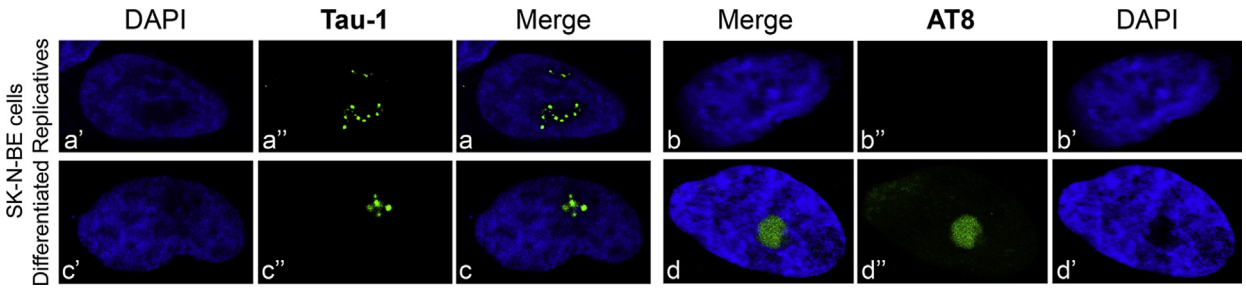

FIGURE 7.3 Tau protein in the SK-N-BE cells. Localization, by immunofluorescence, of Tau-1 and AT8 in the nucleus of replicative and differentiated cells, with AT8 absent in the former (b). Nuclei were stained with DAPI (blue). Scale bars: 5 μm. *From Federico, C., Gil, L., Bruno, F., D'Amico, A. G., D'Agata, V., & Saccone, S. (2018). Phosphorylated nucleolar Tau protein is related to the neuronal in vitro differentiation.* Gene, 664, *1–11.*

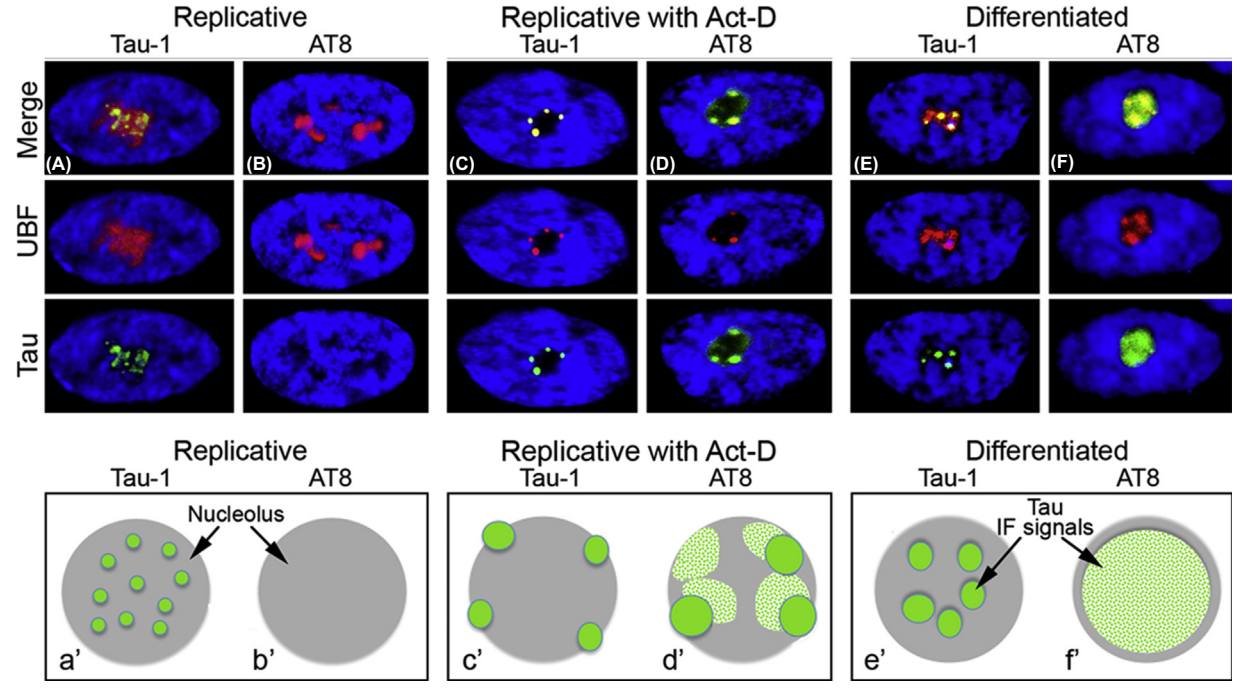

FIGURE 7.4 Tau protein distribution in transcriptionally blocked cells. Colocalization of Tau-1 and AT8 (green signals) with respect to the nucleolar marker UBTF (red signals) after 1 h of actinomycin-D exposure of the cells (c, d) compared to replicative (a, b) and differentiated (e, f) cells. a′ to f′: schematic representation of the nucleolar distribution of Tau epitopes in the cell conditions shown above. Nuclei were stained with DAPI (blue). Scale bars: 5 μm. *From Federico, C., Gil, L., Bruno, F., D'Amico, A. G., D'Agata, V., & Saccone, S. (2018). Phosphorylated nucleolar Tau protein is related to the neuronal in vitro differentiation.* Gene, 664, *1–11.*

phosphoepitope, AT100, corresponding to the pSer212/Thr214 residues, has been detected close to the nuclear global chromatin of human neurons (Hernández-Ortega, Garcia-Esparcia, Gil, Lucas, & Ferrer, 2015; Gil et al., 2017), as well as the nucleus of cultured fibroblasts (Rossi et al., 2008).

The functional role of nucleolar tau

Tau's ability to bind the nucleic acids suggests a role in DNA protection. Indeed, it seems that tau protects dsDNA from thermal denaturation, and from damage induced by free radicals (Camero et al., 2014). Moreover, the reversible and dynamic nature of the tau-DNA interaction suggests a probable role similar to a heat-shock protein. It may act as a stress-response through translocation from the cytoplasm to the nucleus, with nuclear tau under thermal stress seemingly unphosphorylated (Papasozomenos & Su, 1991; Sultan et al., 2011). Another possible role for tau could be facilitating the formation of multiproteic complexes close to DNA promoters and thus acting as a transcriptional activator, due to tau's ability to induce separation of dsDNA versus ssDNA (Krylova et al., 2005).

It is very interesting that tau is located in the nucleolar region, where rRNA genes are actively transcribed, and where tau could act not only in nucleolus assembly and formation but also in rDNA transcription and RNA processing. Moreover, a role in ribosome synthesis may be expected, as well as a role in the correct heterochromatinization of rDNA (Mansuroglu et al., 2016; Sjöberg et al., 2006). Indeed, interactions among tau and perinucleolar heterochromatin could lead to greater stability of the rDNA, especially in the case of illicit recombination (Carmo-Fonseca, Mendes-Soares, & Campos, 2000). Moreover, the association in cell division with NORs suggests a potential role in chromosomal stability (Bukar Maina et al., 2016), thus at present, a number of roles could be suggested for nuclear/nucleolar tau. It may be that tau in the nucleus is involved in a number of different activities related to transcriptional regulation of rDNA, ribosomal biogenesis, heterochromatin organization, and DNA protection. This could be possible considering the high number of epigenetic modifications described in the tau protein and the different numbers of isoforms obtained by alternative splicing.

Tau protein and cell aging

Nuclear tau and neurodegeneration

A number of studies have reported a reduction in the NORs and in rDNA transcription during neurodegeneration. This is in addition to a reduction and alteration in the machinery regulating ribosomal biogenesis such as UBTF, nucleolin (NLC), and nucleophosmin (NMP1) in some regions of the brain in AD (Ding, Markesbery, Chen, Li, & Keller, 2006; Hernández-Ortega et al., 2015), and specifically in the CA1 and the Dentate Gyrus (DG) regions of the hippocampus. As described above, nucleolar tau seems to be involved in rRNA biogenesis, and its hyperphosphorylation should lead rDNA altered expression, as observed in AD (Lu, Miao, Su, Liu, & He, 2013).

The involvement of nuclear tau in neurodegeneration seems to be due to hyperphosphorylation and aggregation. It has been recently demonstrated that hyperphosphorylation plays a relevant role in oxidative stress induction, dsDNA breakage, heterochromatin decondensation, deregulation of gene expression, and re-entry into the cell division cycle (Frost, Hemberg, Lewis, & Feany, 2014; Mondragón-Rodríguez et al., 2013). Thus, neurodegeneration could be related to a possible protective response of the cell to a number of different stressors, beginning with reactivation of the nucleolus followed by reactivation of the cell cycle, an event that cannot proceed further, due to the differentiated status of the cell.

Nuclear tau in replicative and differentiated cells during aging

The phosphoepitope AT100, detected close to the nuclear global chromatin of human neurons, was also observed to increase during aging in the nucleus of neurons from DG and CA1 regions of the human hippocampus, and the interaction between AT100 and global chromatin progressively decreases until it disappears in more advanced stages of AD (Hernández-Ortega et al., 2015; Gil et al., 2017) (Fig. 7.5 and 7.6). This suggests a close relationship between Ser212/Thr214 phosphorylated tau (AT100) and heterochromatin loss, global chromatin relaxation, and gene expression deregulation in AD (Frost et al., 2014). It should be clarified that tau protein has not only been related to AD but also to cancer, both age-related diseases, and it has been suggested that aging may activate similar pathways in both cases (Souter & Lee, 2009). It is well known that nuclear aging is associated with chromatin damage and genomic instability (Lenart & Krejci, 2016; Pegorano & Misteli, 2009), characterized by changes in chromatin structure, such as heterochromatin loss (Tsurumi & Li, 2012) and aging of the transcriptional profile (Lu et al., 2004).

The presence of AT100 in the nucleus could be related to a protection effect on the genome, and the increased level of the protein related to cell aging could be due to a higher amount of the protein necessary to protect DNA from the accumulation of damages occurring during cell life. In this regard, a large amount of evidence, as described above, indicates that tau is an

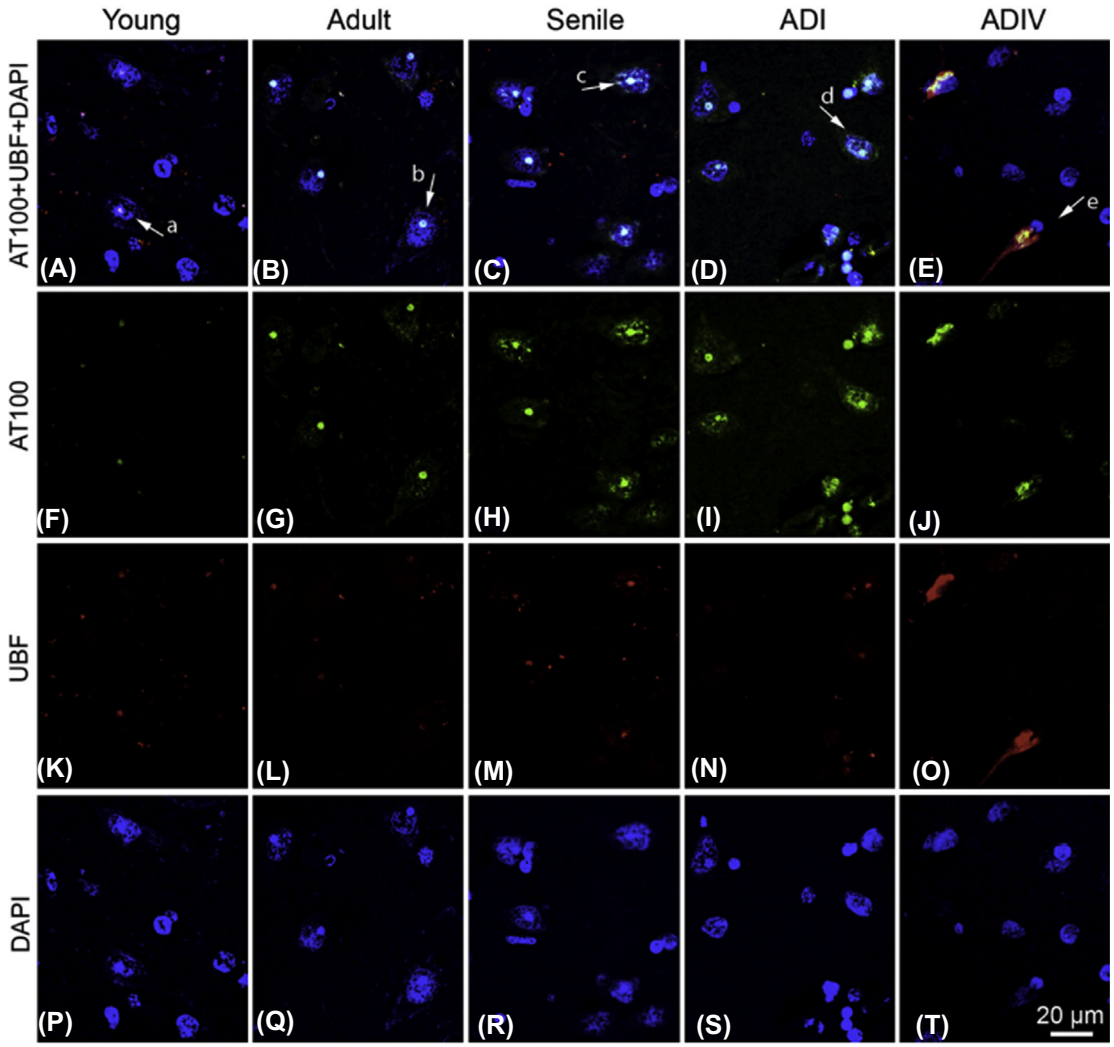

FIGURE 7.5 AT100 epitope in pyramidal neurons from the CA1 region. Pyramidal neurons from the CA1 region of young (20–40 years) (A), adult (40–60 years) (B), senile (more than 60 years) (C), ADI (D), and ADIV (E) brains, respectively. AT100 (green signals) colocalize with the nucleolar marker UBTF, previously called UBF (red signals) in the nucleolus and increases from young to senile brain cells. White arrows (a, b, c, d, e) indicate the colocalization of AT100 and UBTF in the nucleolus. Nuclei were stained with DAPI (blue). ADI and ADIV indicate the I and the IV stage of the Alzheimer disease. Scale bar, shown in panel T: 20 µm. *From Gil, L., Federico, C., Pinedo, F., Bruno, F., Rebolledo, A. B., Montoya, J. J., … Saccone, S. (2017). Aging dependent effect of nuclear tau.* Brain Research, 1677*, 129–137.*

important protein connected to DNA stabilization and protection. It has been reported that tau binds DNA inducing conformational changes, protecting it from a number of stresses such as oxidative stress, and making the DNA more stable (Krylova et al., 2005; Padmaraju, Indi, & Rao, 2010; Qu et al., 2004; Sultan et al., 2011; Wei et al., 2008).

The increase in AT100 interaction with global heterochromatin is strikingly different in aging proliferative cells, such as epithelial cells and granular neurons (Fig. 7.6), compared to the differentiated cells such as pyramidal neurons (Fig. 7.5). In the former, AT100 forms large blocks of aggregated protein whereas in the latter it is more diffuse in the nuclei with a few large blocks of aggregation (Gil et al., 2017). The reprogramming of chromatin during aging seems to be different in proliferative versus differentiated cells as well, and this difference may be due to chromatin organization of these cells after the start of differentiation, and the repair mechanisms become less efficient than stem cells (Sykora et al., 2013; Zeng, 2007). This is especially true if the DNA double-strand break (dsb) repair mechanism is considered in the context of the different types of chromatin organization, as a higher resistance at dsb mutations in the more compact heterochromatin has been observed (Falk et al., 2014; Goodarzi, Jeggo, & Lobrich, 2010). It has been proposed that the AT100 phosphoepitope could interact with repetitive DNA from interphasic chromatin to maintain the more compacted status. Thus, amounts of this phosphoepitope increase with the increasing level of mutation/alteration affecting the more compact chromatin positioned at the nuclear periphery during aging.

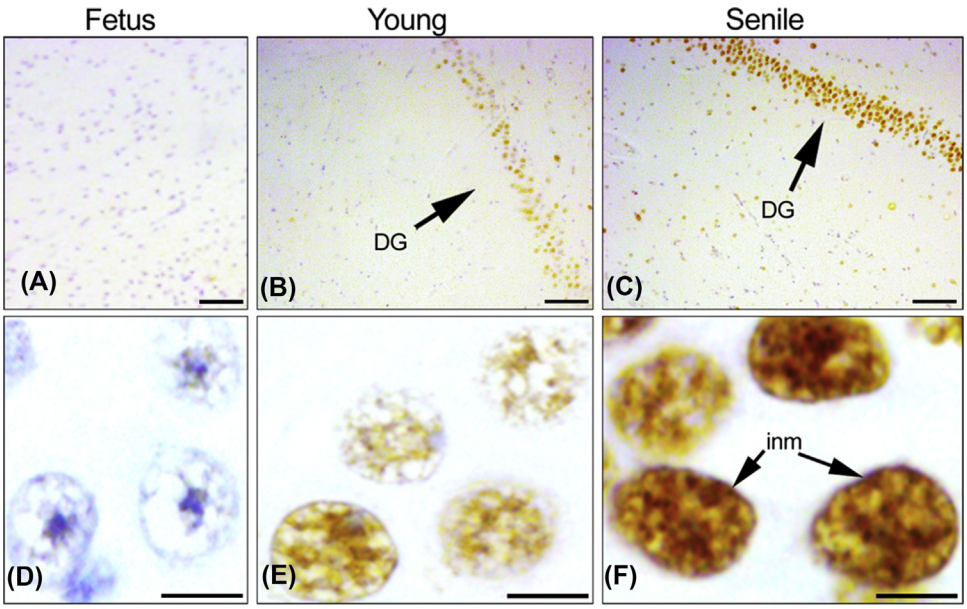

FIGURE 7.6 AT100 epitope in granular neurons of the hippocampus at different ages. Immunohistochemistry analysis of AT100 in granular neurons from the dentate gyrus of fetus (8–12 weeks) (A, D), young (20–40 years) (B, E), and senile (more than 60 years) (C, F) brains. The amount of AT100 increases during aging in the cell nuclei of the granular neurons. DG: dentate gyrus; inm: inner nuclear membrane. Scale bar in (A–C): 100 μm; in (D–F): 10 μm. *From Gil, L., Federico, C., Pinedo, F., Bruno, F., Rebolledo, A. B., Montoya, J. J., … Saccone, S. (2017). Aging dependent effect of nuclear tau.* Brain Research, 1677, *129–137.*

Nuclear tau and aging pathology

For decades, it has been thought that the CA1 region in AD is related to the degeneration of the cytoskeleton of pyramidal neurons from the hippocampus, and granular neurons from DG. Both disorders are involved in the progressive atrophy of hippocampus and memory loss observed in AD patients (Llorens-Martín et al., 2014).

Nevertheless, more recent results have revealed a strong conformational change in global chromatin in pyramidal neurons in early AD, which is maintained throughout the development of the disease (Frost et al., 2014). This change has also been observed in granular neurons of the DG, although differences between the neurons from the hippocampus and from the DG have been reported (Hernández-Ortega et al., 2015).

In addition, a gradual modification of chromatin in relation to nuclear tau, identified by the AT100 epitope, occurs during human adult neuronal life development reaching a maximum degree in aging neurons. A dramatic nuclear change takes place between aging neurons and AD neurons, possibly related to an aberrant attempt to re-enter the cell cycle associated with aging stress (Zhu, Raina, & Smith, 1999). However, the neuron is a nonreplicative cell and cannot develop a tumoral process; therefore, this event may begin the neurodegenerative process associated with age in this area of the brain (Bonda et al., 2009; McShea et al., 2007). In this sense, the changes observed in the conformation of global chromatin in relation to nuclear tau in aging cells with respect to younger cells, and even more so, to AD neurons, should be directly associated with alterations in gene expression (Lu et al., 2004).

Applications to other areas of aging

Phosphorylation of nuclear tau in Ser212/Thr214 residues (AT100) determines its interaction with global chromatin, and this interaction seems to be enhanced during chromatin reprogramming associated with aging. The increased level of AT100, in the AT-rich chromatin localized at the nuclear periphery, may play a role in the maintenance of genomic stability (possibly via interactions with the repetitive DNA present in this genomic compartment) and in the regulation of genes involved in cellular aging. However, further research is needed to determine whether nuclear tau could be considered a true aging marker.

It has been described that neurons during aging and neurons from AD undergo relevant nuclear alterations, such as the aberrant attempt to start the cell division cycle. Nevertheless, a neuron is a terminal differentiated nonreplicative cell that cannot develop a tumor process. Thus, this event could be the starting point for neurodegenerative age-related processes,

namely cell degeneration and uncontrolled proliferation. These are two different ways that cells can undertake processes related to aging diseases, such as AD and cancer (Navarrete-Reyes, Soto-Perez de Celis, & Hurria, 2016). A number of researchers, taking into consideration that AD subjects very rarely develop cancer, and that subjects with cancer present a very low risk for AD, hypothesized an inverse association between neurodegeneration and cancer (Driver, 2014). Moreover, other evidence indicates that AD and cancer are two pathologies involving deregulation of similar molecular mechanisms, and that alteration in the nuclear chromatin organization seems to be a common feature between them. Further work to enhance our knowledge on cell aging should be directed toward the better understanding of genome organization in cells with different features comprising both physiologic and pathologic conditions. Such studies can now be carried out by combining a variety of molecular genetic, biochemical, and histological procedures, such as immuno-localization, DNA and RNA fluorescence in situ hybridizations, organization of genomic TADs obtained by HiC, and 3D reconstruction. Improving collaborations among researchers working in these different areas would be a step toward understanding cell processes during normal cell aging and the deregulation of this physiological process.

Key facts of neurodegeneration

- Neurodegeneration is the gradual loss of neurons' structure and function until cell's death.
- The molecular process of neural degeneration is not yet clearly understood and its molecular markers are still unknown.
- Aging is a main risk factor for neurodegenerative diseases such as AD.
- Neurodegenerative disorders are becoming more and more common among older people due to aging of global population.
- Neurodegeneration is related to the gradual accumulation of protein aggregates that are cytotoxic for neurons, such as the intracellular NFTs and the extracellular amyloid plaques in AD.
- An aberrant cell cycle reboot in neuronal cells seems to occur both in neurodegeneration and aging.
- Neurodegeneration and cancers are two alternative fates that can be taken by cells; there seems to exist a reverse correlation between them but they seem linked to the same molecular pathways of aging.

Summary points

- *MAPT* gene codifies the six isoforms of tau ranging from 352 to 441 amino acids, obtained by alternative splicing of exons 2, 3, and 10.
- Microtubule binding domain of tau is composed of three (isoform 3R) or four (isoform 4R) repeats, in the C-terminal part of the protein.
- The N-terminal part of tau interacts with cytoskeleton proteins via an acidic-rich domain endowed with a variable length in the different isoforms 0N, 1N, and 2N.
- Tau presents 85 potentially phosphorylatable sites and hyperphosphorylated tau was observed in the hippocampus region of AD brains.
- Nuclear tau was detected in the nucleolus, colocalizing with the transcriptional factor UBTF.
- AT100 epitope of tau increases with aging, reaching a maximum level at the senile stage and drastically decreasing in AD.
- AT8 epitope of tau in absent in replicative cells and appears in the differentiated ones.

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