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REVIEW

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Neuronal nuclear tau and neurodegeneration

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Abstract—Tau is a well-known microtubule-associated protein related to its cytoplasmic localization in a neuronal cell. However, tau has been located at the cell nucleus where it could be a nucleic acid-associated protein by its preferential binding to DNA sequences present in the nucleolus and pericentromeric heterochromatin. This less well-known localization of tau could not be trivial, since during aging, an increase in the amount of nuclear tau takes place and it may be related to the described role of tau in the activation of transposons and further aging acceleration.

Key words: Aging, Neurodegeneration, Nucleolus, nucleus, nuclear pore, Tau.

INTRODUCTION

Human tau protein isoforms are expressed from a unique gene (mapt) located at chromosome 17 (Neve et al., 1986; Himmler, 1989). Mapt has 16 exons (Andreadis et al., 1992; Andreadis, 2005), but in CNS only exons 1,4,5,7,9,11,13 and 14 are constitutive, while the rest could be subjected to alternative splicing (Andreadis, 2005; Wang and Mandelkow, 2016). The presence or absence of a specific exon, like exon 10, could be associated with the development of some tauopathies (Goedert et al., 1998; Hutton et al., 1998; D'Souza et al., 1999; Fernandez-Nogales et al., 2014). Recently, related to a mechanism different to alternative splicing, known as intron retention, a new human isoform, expressing a sequence of intron 12 and lacking exon 13 has been described. It is not known if this isoform could accumulate or not during aging, as occurs for other isoforms in other tauopathies (Gil et al., 2017).

Aging is the main risk factor for neurodegenerative disorders such as Alzheimer disease (AD), the most prevalent tauopathy characterized by the presence of two main hallmarks, senile plaques formed of amyloid peptide aggregates and neurofibrillary tangles composed of tau protein (Masters et al., 2015). During aging, an accumulation of tau can be found in the cell nucleus (Guo et al., 2018). Indeed, there are some differences in the presence of specific tau isoforms at the cell nucleus (Liu and Gotz, 2013). Also, post-translational modification of tau isoforms can favor the interaction of the protein with membranes (Arrasate et al., 2000) or increase its presence in dendrites (Llorens-Martin et al., 2013).

The nucleus contains the genetic material of the cell. The nucleus is separated from the cytoplasm by a double membrane called the nuclear envelope that is contiguous with the rough endoplasmic reticulum. The nuclear envelope has complex nuclear pores that control nucleocytoplasmic transport. The nuclear lamina, which is located on the inner face of the nuclear envelope, serves as a mechanical support and participates in the organization of the chromosomes that, in interphase, occupy differentiated territories. The interchromatin space is not unstructured and is organized in dynamic nuclear bodies, such as Cajal bodies, nuclear speckles, nucleoli, paraspeckles, perinucleolar compartments, PML (Promyelocytic leukemia) nuclear bodies, Polycomb bodies and clastosomes (for a review see (Mao et al., 2011)).

In this review, we have focused on nuclear tau, its preferential localization in regions like the nucleolus or pericentromeric chromatin, and on its interaction with nuclear components like proteins and, mainly, nucleic acids. Finally, we have commented about the role, related to cell aging, of tau in the activation of transposons expression.

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Abbreviations: AD, Alzheimer disease; FD, Frontotemporal dementia; HGPS), Hutchinson-Gilford progeria syndrome; L1, LINE1; LTP, Long-term potentiation; NL, nuclear lamina; PCH, pericentromeric heterochromatin structures; piRNAs, Piwi-interacting RNAs; rDNA, ribosomal DNA; SD, sleep deprivation; snRNAs, small nuclear RNAs; snoRNAs, small nucleolar RNAs; TEs, transposable elements; H3K9me3, trimethylated form of lysine 9 of histone H3; UBF, upstream binding transcription factor.

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TAU BINDING TO CHROMATIN AND NUCLEIC ACIDS

The *in vitro* binding of microtubule proteins to DNA and chromatin, including tau protein, was reported a long time ago (Villasante et al., 1981). Although the binding to DNA has been studied in detail (Wiche et al., 1978; Villasante et al., 1981), recent *in vivo* analysis demonstrated the co-localization of tau with chromatin proteins like HP-1, a pericentromeric heterochromatin protein (Mansuroglu et al., 2016). This suggested the potential interaction of tau with protein chromatin components besides its interaction with DNA (Sultan et al., 2011).

Preferential binding of tau to GC-rich or AT-rich DNA regions has been reported (Sjoberg et al., 2006; Maina et al., 2018). Thus, nucleolus contains the ribosomal DNA (GC rich regions) (Maina et al., 2018) or the pericentromeric α-satellite DNA (AT-rich regions) (Wiche et al., 1978; Sjoberg et al., 2006).

Binding of tau to RNA has been also reported and this interaction may facilitate tau protein aggregation (Kampers et al., 1999). In this way, tau aggregates contain RNA with an enrichment of small nuclear RNAs (snRNAs) and small nucleolar RNAs (snoRNAs) (Lester et al., 2021). It should be analyzed if, among those snRNAs, Piwi-interacting RNAs (piRNAs) may be included (Ozata et al., 2019).

On the other hand, tau oligomers mediate the aggregation of RNA-binding proteins (Montalbano et al., 2019). Furthermore, a role for RNA-tau complexes in the formation of liquid–liquid phase separation has been suggested (Ash et al., 2021). In addition, the binding of tau to methyl-adenosine modified RNA transcripts has been indicated (Jiang et al., 2021). All these interactions seem to be related to the progression of tauopathy.

TAU ENTRY TO THE NUCLEUS

Different tau isoforms show different cell localization, being the isoforms containing exon 2 those that are mainly located at the cell nucleus (Liu and Gotz, 2013). However, those tau isoforms lack any nuclear localization signals that would allow their transport from the cytoplasm to the nucleus. Also, exon 2, the marker for those isoforms, has several acidic residues that may result in a negatively charged region. Thus, it should be analyzed if the exon 2 region can bind to a basic protein to favor its transport to the nucleus. Indeed, none of the different human tau isoforms show a nuclear localization signal to allow its transport through the nuclear pores to inside the nucleus, although, tau mutation N279K increases nuclear localization (Ritter et al., 2018).

On the other hand, tau protein disrupts nucleocytoplasmic transport in pathologies like Alzheimer disease through its direct interaction with nucleoporins present in the nuclear pore complex (Eftekharzadeh et al., 2018). Indeed, nucleoporin Nup98 for example can bind to tau to facilitate its aggregation *in vitro* (Ritter et al., 2018). Despite all above possibilities, at the present, we do not know yet how the transport of tau to the cell nucleus takes place. Thus, further research would be needed to answer this relevant question.

Tau at Nuclear lamina (NL)

The inner nuclear membrane of animals is lined by a scaffold structure named nuclear lamina (NL) which connects the nucleoskeleton with the cytoskeleton. It is a flexible protein network mainly made up of type V intermediate filament proteins called lamins, whose combination is variable and which confer different mechanical properties (van Steensel and Belmont, 2017; Nmezi et al., 2019). The finding of Tau adjacent to the inner side of the NL (Gil et al., 2017; Eftekharzadeh et al., 2018) regulating nuclear pore complex pointed out a nuclear role for tau (Gil et al., 2021).

The relationship between tau and NL has been demonstrated by different studies. The expression of full-length tau or Asp421 truncated tau in neuroblastoma cells led to nuclear envelope invaginations coupled with a lobulated nuclear form, similar to lamin-mutated cells from prematurely aged mice (Monroy-Ramirez et al., 2013). Regarding nuclear invaginations, they have been found to be filled by tau nuclear rods in neuropathologies like Hungtington disease or frontotemporal dementia (Fernandez-Nogales et al., 2014; Paonessa et al., 2019). In addition, tau has been seen regulating nuclear Lamin B1 protein expression (Frost et al., 2014; Frost, 2016), and more recently it has been found that pathological tau through its association with a ribosomal binding protein called Musashi, is able to reduce Lamin B1 protein levels disrupting the nuclear lamina architecture (Montalbano et al., 2019). Likewise, tau mutant P301L transgenic mice showed also disruption of NL (Eftekharzadeh et al., 2018). One of the consequences of NL architecture impairment seems to be the disruption of nucleocytoplasmic transport, which has been related to both overexpressing tau and with the presence of pathological tau (Frost, 2016; Eftekharzadeh et al., 2018).

Changes in NL are considered a typical sign of aging. In fact, the accelerated aging disorder Hutchinson-Gilford progeria syndrome (HGPS) is considered a laminopathy due to mutant lamin A/C protein (Oberdoerffer and Sinclair, 2007). Alterations at NL have been described in brains from AD patients (Frost, 2016; Gil et al., 2021) where neurons showed a more complex NL structure than in normal aged neurons. Thus, it has been described that lamin A protein is incorporated into this structure, which in healthy neurons is normally absent (Mendez-Lopez et al., 2019). This lamin protein increases the rigidity of NL and alter chromatin consistency (Wintner et al., 2020). In fact, the function of NL cannot be reduced solely to be an architectonic scaffold, but NL has a relevant role in regulating genetic expression (Martins et al., 2020). Alterations in the nuclear architecture can induce changes in the organization of DNA, through modifications in nuclear pores which can modify the transit of regulating factors to the nucleus. This would explain why different studies have pointed out that epigenetic changes can be driven by alterations at lamin proteins levels.

Nuclear tau-localization (nucleolus)

From the seminal work carried out the group of Binder indicating the presence of tau in the nucleolus (Loomis

et al., 1990), two main localizations have been found for nuclear tau, the nucleolus (Loomis et al., 1990; Diez and Wegmann, 2020) and the pericentromeric heterochromatin (Mansuroglu et al., 2016).

The presence of Tau at nucleolus, localizing at the dense fibrillar regions or to the nucleolar organizer region of mitotic chromosomes, has been widely reported mainly by Tau-1 immunofluorescence (Loomis et al., 1990; Wang et al., 1993; Thurston et al., 1996). Indeed, as with other typical nucleolar proteins, Tau seems to undergo a stress-induced redistribution within the nucleolus. In fact, nucleolar stress signatures in different AD brain regions were associated with reduced levels of different nucleolar proteins including nuclear tau (Hernandez-Ortega et al., 2016).

Nuclear studies have pointed out an important role of Tau in nucleolar structure conformation (Sjoberg et al., 2006; Rossi et al., 2008). Tau colocalizes with other relevant nucleolar proteins such as nucleolin, upstream binding transcription factor (UBF), or TIP5 in cell cultures and in human brain tissue (Sjoberg et al., 2006; Maina et al., 2018).

Since nucleolus is the most important center for rRNA gene metabolism, the presence of Tau in that localization suggested its likely involvement in ribosomal DNA (rDNA) transcription and ribosome synthesis. In fact, it has been found that human tau can interact with both rRNA and ribosomes mainly through its association with RNA-binding proteins (Meier et al., 2016; Banerjee et al., 2020). The interaction of tau with ribosomes in the brain is further enhanced in tauopathies (Meier et al., 2016), showing an impaired functioning presumably due to the formation of a complex between hyperphosphorylated tau and ribosomes in both, neurons and astrocytes (Papasozomenos and Binder, 1987; Papasozomenos, 1989; Papasozomenos and Su, 1991).

In addition, tau can bind to DNA (Wiche et al., 1978), and specifically, it has been found to bind to the promoter regions of rDNA loci, showing a potential role in the regulation of transcription processes (Bou Samra et al., 2017). Altering tau expression via the use of tau knock-out mouse models, it was possible to confirm its involvement in transcription regulation. Tau depletion induced a decrease in rDNA transcription, and specifically of 45S-pre-rRNA, due to the reducing recruitment of UBF protein to rDNA (Bou Samra et al., 2017).

Since tau interacts with different key elements of the translational machinery, it was expected that it would have an influence on protein synthesis. Indeed, it has been found how tau-K174 acetylation cause its translocation to the nucleus, regulates rRNA production and ultimately it results in the increase of protein synthesis (Portillo et al., 2021). The exacerbation of this same process seems to happen in aging and especially in Alzheimer disease patients, where it has been found a significative nuclear accumulation of tau-K174ac along with increased nucleolar proteins and with a reduction of the deacetylase protein SIRT6 (Portillo et al., 2021).

Another study also found a relevant negative impact of pathologically phosphorylated tau on protein synthesis in an age-dependent manner (Evans et al., 2021). They found in neurons from transgenic mice expressing K368I or P301L mutant tau and in human FTD brains significant reduction in protein synthesis including ribosomal proteins such as 60S and 40S ribosomal subunit proteins or in histone proteins like H3. Despite the general reduction, some proteins were found to increase their expression like histone 4 protein.

Recently it has been found another important link between AD and pathological tau, in which its nucleolar role seems to have special relevance. The ribosomal protein pS6 has been found colocalizing with pathological tau in AD brains, inducing a decrease of S6 function by preventing its phosphorylation (Koren et al., 2019). Since pS6 is involved in the regulation of ribosomal protein synthesis, its loss of function by tau in AD brains could be behind the loss of translation and protein synthesis found in AD and tauopathies (Meier et al., 2016). Additionally, the reduction of pS6 levels correlate with dendritic atrophy and with LTP impairment, therefore the altered function of that protein by pathological association with tau could be involved in cognitive disfunctions described in tauopathies (Meier et al., 2016). Furthermore, sleep deprivation (SD) episodes have been described in AD (Moran et al., 2005; Tractenberg et al., 2006), and studies in a tau knockout mice model found a role of this protein in sleep-wake regulation (Cantero et al., 2010). Since SD seem to interfere with the increased protein synthesis needed for learning (Tudor et al., 2016), and to decrease the ribosomal protein pS6 expression in the hippocampus (Delorme et al., 2021), pathological nuclear tau could be behind sleep disturbances described in tauopathies like AD through its action in ribosome proteins like pS6. At this point, further experiments will be needed to know if that is the case.

TAU AND PERICENTROMERIC HETEROCHROMATIN

In neuronal cells, centromeric regions, which are composed of repeated satellite DNA, are localized at the surface of the nucleolus, normally forming a ring of nuclear heterochromatin (Sjoberg et al., 2006). It has been suggested that these pericentromeric heterochromatin structures (PCH) could be regulating nucleolus functioning (Carmo-Fonseca et al., 2000), and tau seems to be a link between both elements. In neurons, nuclear tau has been found within or close to PCH, colocalizing and binding to pericentromeric AT-rich satellite DNA sequences (Sjoberg et al., 2006; Mansuroglu et al., 2016). In addition, tau has been characterized as regulating PCH structure (Sjoberg et al., 2006), which essential role in gene expression point out again the role of tau in gene regulation.

The involvement of tau in PCH structure was tested in a tau-KO transgenic mouse model, where tau depletion led to the alteration of PCH stability, being possible to reverse it by tau overexpression (Mansuroglu et al., 2016). Heterochromatin stability would be partially regulated by the interaction of the trimethylated form of lysine 9 of histone H3 (H3K9me3) and heterochromatin protein 1α (HP1α), both hallmarks of PCH. It has been suggested

that tau could be involved in addressing HP1α and, through this action, influence H3K9me3 nucleation within PCH (Hiragami-Hamada et al., 2016). In fact, the distribution of both H3K9me3 and HP1α is severely disrupted by tau depletion. These alterations induced by tau depletion consisted in enhanced diffuse distribution of HP1α and reduced clusters of H3K9me3 marks within the nucleolus, being even found some of these marks in the cytoplasm. Moreover, these alterations resemble the changes found during PCH reorganization in undifferentiated embryonic stem cells (ES), in this case likely associated with their pluripotency state (Mansuroglu et al., 2016).

The loss of heterochromatin due to tau depletion, showed by the reduction of different epigenetic marks involved in chromatin silencing such as H3K9me3, H3K9me2, or 5-methylcytosine (Maina et al., 2018), highlight the role of tau in the regulation of gene expression.

In addition, the disruption of the H3K9me3 epigenetic marker in tau KO mice led to a displacement of phosphorylated H2AX protein from PCH to the cytoplasm. As H2AX protein has a relevant function in double-strand break repairment, neurons lacking tau protein showed an aberrant ability to repair PCH heat shock-induced DNA breaks (Mansuroglu et al., 2016). This reveals a protective role of nuclear tau during stress events and its loss of function during tauopathies could have a relevant negative impact on nuclear functioning. In fact, the effects of pathologic tau in PCH organization were even more exacerbated in hippocampal neurons from AD brains than those found by tau depletion. In these cells, H3K9me3 marks were found in the cytoplasm along with a disrupted PCH integrity (Mansuroglu et al., 2016). In addition, it was found a correlation between tau pathology and chromatin relaxation (Frost et al., 2014; Guo et al., 2018). For example, in AD patients tau acetylated at K174 residue has been found associated with H3K9 acetylated epigenetic mark in open chromatin (Portillo et al., 2021). Since AD and aging exhibit increased levels of retrotransposons and open chromatin due to the loss of heterochromatin (Guo et al., 2018; Sun et al., 2018) and PCH-associated proteins like HP1, the role of tau in age-associated chromatin alterations should be further considered.

NUCLEAR TAU AND AGING

Nuclear tau, phosphorylated at its threonine 212, increases its amount during aging in the nucleolus and pericentromeric heterochromatin of pyramidal neural cells present at CA1 region, being the highest accumulation of nuclear tau in senescent cells (Gil et al., 2017). However, the presence of that phosphorylated tau decreases, in Alzheimer disease (AD), at its later stages (Gil et al., 2017).Since Thr212 is modified by the kinase GSK3β (Timm et al., 2008), and the activity of this kinase increases with age and AD pathology (Timm et al., 2008; Souder and Anderson, 2019; Lauretti et al., 2020), a possible way to explain the increase of phosphorylated nuclear tau with aging may be related to the increase of GSK3β.

AGING AND TRANSPOSONS

In contrast to the initial idea that the neuronal genome was a static entity, there are now many data showing that a rearrangement of DNA transposons happens and modulates genome stability and expression in neurons, during their lifetime.

Transposable elements (TEs) are defined as mobile DNA elements able to change their localization within a genome (Andrenacci et al., 2020). There are two main classes: Class I, the transposons which use DNA as intermediate (DNA transposons) to make a ‘‘cut-and-paste” mechanism, and class II, the retrotransposable elements (retrotransposons), which move using an RNA intermediate in a ‘‘copy-and-paste” mechanism (Sun et al., 2018). The presence of transposons of both classes in adult neurons of human brains has been documented ten years ago (Baillie et al., 2011).

Regulation of TEs expression is related to condensation/decondensation of the heterochromatin. As we have mentioned above, heterochromatin relaxation is associated with agind and AD. Therefore, the activation of TEs expression can lead to greater instability of the genome and transcriptional dysregulation. This expression is inhibited by events such as clearance of TEs via Piwi-interacting RNAs (piRNAs) (Brennecke et al., 2007; Gorbunova et al., 2021).

It has been suggested that the increased activation of TEs in somatic tissues, taking place during aging, reduces life span (Driver and McKechnie, 1992). The role of TEs in aging and their possible involvement in laminopathies has been suggested. Lamin A/C depletion is associated with the activity of LINE1 (L1), a retrotransposon present in human cells (Lauretti et al., 2020). In addition, TEs activation is related to the Piwi-piRNA pathway (Sturm et al., 2017). In this way, piRNA can recruit chromatin factors needed for TEs activation. In that process, piRNA binds to its target transcripts (Gorbunova et al., 2021), contributing to post-transcriptional silencing of the transcript. A decrease with age of the Piwi-piRNA pathway results in the loss of silencing and TEs activation (Sturm et al., 2017).

TAU AND TRANSPOSONS

Lately, two different groups reported the abnormal TEs activation in post-mortem AD brains and in *Drosophila* transgenic models expressing wild type or mutated (R406W) tau (Galas et al., 2019). Guo et al., 2018 and Sun et al., 2018 reported tau as the responsible for TEs activation and genomic instability associated with AD, and not the consequence of this activation (Guo et al., 2018; Sun et al., 2018). But Sun and collages go further and demonstrate that piRNAs levels vary depending on tau. In their *Drosophila* transgenic model, they observed first a decrease in Piwi/piRNAs along with the condensation of the heterochromatin and, in second place, an increase in the deregulation of TEs, linking these events with the neuronal dead characteristic of tauopathies. Because Piwi-protein and piRNAs are involved in nuclear metabolism and tau is also in the nucleus, tau might be involved in this process more directly than previously thought.

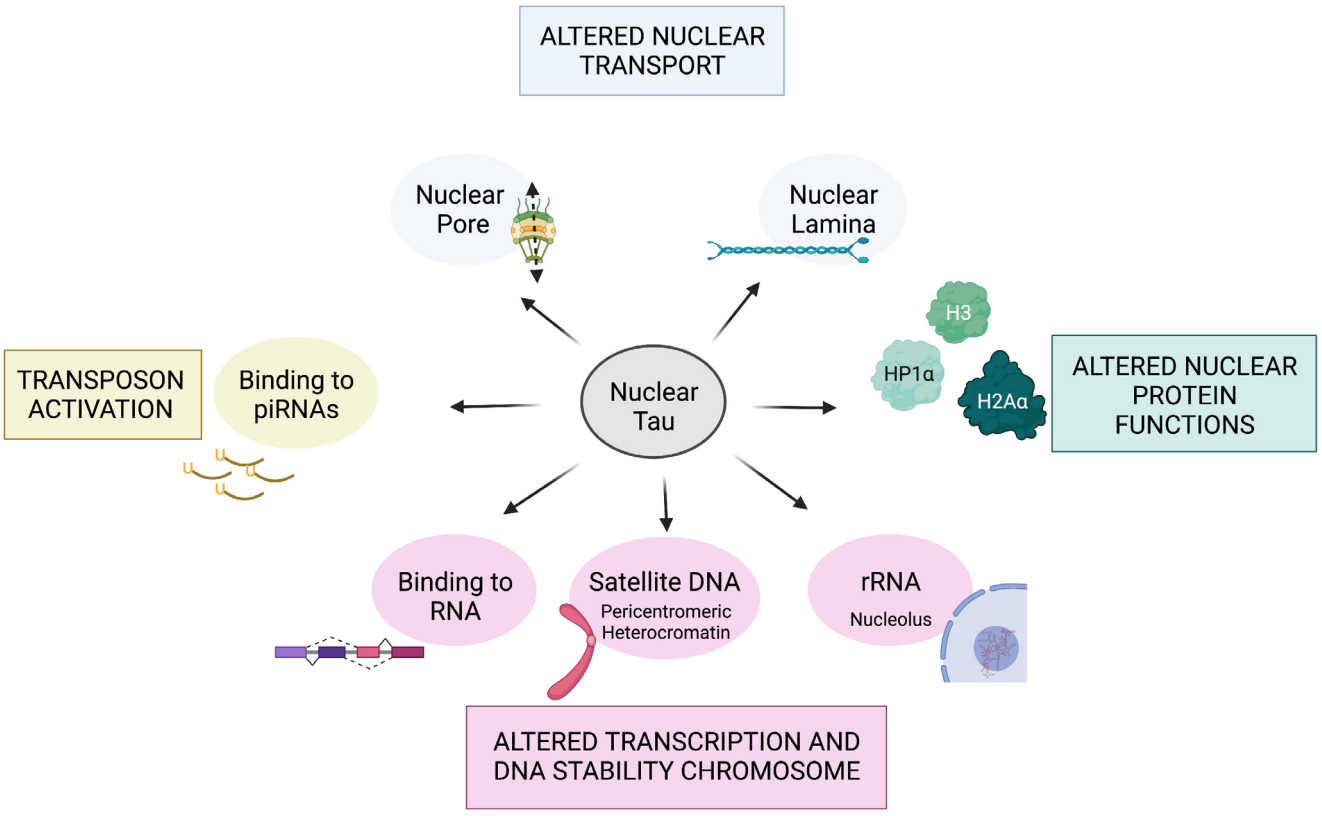

Fig. 1. A working hypothesis to explain the role of aging-related nuclear tau accumulation in neurodegeneration. Tau has been mainly localized to the nucleolus but has also been shown to bind to DNA and RNA, suggesting that it might regulate chromosome stability and transcription probably through nuclear chromatin proteins. Aging and pathogenic tau modify these functions as well as nuclear transport and probably transposon activation.

Also, pathogenic tau accelerates the aging-associated activation of TEs in the mouse central nervous system (Ramirez et al., 2022), resulting in an increase of transposon transcripts and their encoded proteins. An example is LINE1 (L1), a retrotransposon that comprises more than 15 % of the human genome (Lander et al., 2001). L1 transcript contains two non-overlapping open reading frames; ORF1 and ORF2. Translated ORF1 results in a RNA binding protein (Martin, 2006), whereas ORF2 encodes a protein with an endonuclease and reverse transcriptase activity (Gorbunova et al., 2021).

A possible role of tau as a RNA binding protein could be suggested in the mechanism involving ORF1 and ORF2 proteins in retrotransposition. In that mechanism, tau could complement the ORF1 encoded protein by binding to the same RNA molecules.

Tau protein have different cellular localizations associated with different cellular functions. Thus, tau in the cytoplasm of a neuron is primarily a microtubule-associated protein (linked with tubulin). However, the presence of tau in the cell nucleus, which lacks tubulin, could be explained by an alternative role of tau as a nucleic acid-associated protein. This has been proposed since tau may be associated with regions of ribosomal DNA or with satellite DNA present in pericentromeric chromatin. However, other possible functions (or dysfunctions) of tau due to its presence on the nucleus have been discussed. All recent findings about tau nuclear functions described in this article open new questions to solve, for example how tau moves from the cytoplasm to the nucleus. This could be relevant for brain aging, since nuclear tau seems to accumulate in neurons, accelerating, eventually, aging process or having toxic consequences (see Fig. 1). Currently, clinical trials targeting the tau protein are fundamentally based on immunotherapies. Since tau pathology correlates better with cognitive impairments than senile plaques, the other main neuropathological hallmarks of AD, the results are expected to be more promising. In this sense, the knowledge we have of the physiological functions of nuclear tau is still scarce, and it is necessary to better understand these functions and how they are altered in the disease to exploit nuclear tau for the treatment of neurodegenerative disorders. Furthermore, increasing our knowledge about nuclear functioning of tau may help to understand relevant processes like aging and for that reason it should be considered more closely in further studies.

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