Editorial Special Issue Neuroscience ‘‘Tauopathies”

Jesus§ Avila,[a,b*] Ismael Santa-Maria[c,d,e] and Ioannis Sotiropulos[f,g,h]

[a] *Centro de Biologı´a Molecular Severo Ochoa (CSIC-UAM), 28049 Madrid, Spain*

[b] *Networking Research Centre on Neurodegenerative Diseases (CIBERNED), 28031 Madrid, Spain*

[c] *Facultad de Ciencias Experimentales, Universidad Francisco de Vitoria, Edificio E, 28223, Pozuelo de Alarcon, Madrid, Spain*

[d] *The Taub Institute for Research on Alzheimer’s Disease and the Aging Brain, Columbia University Medical Center, 630 West 168th Street, New York, NY 10032, USA*

[e] *Department of Pathology and Cell Biology, Columbia University Medical Center, 630 West 168th Street, New York, NY 10032, USA*

[f] *Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal*

[g] *ICVS/3B’s – PT Government Associate Laboratory, Braga/Guimara˜es, Portugal*

[h] *Institute of Biosciences and Applications NCSR ‘‘Demokritos”, Athens, Greece*

*Correspondence to: Jesus§ Avila, Centro de Biologıá Molecular Severo Ochoa (CSIC-UAM), 28049 Madrid, Spain.
E-mail address: javila@cbm.csic.es (J. Avila).

Tau is a brain microtubule associated protein (Weingarten et al., 1975) that is expressed, from a single gen (Neve et al., 1986), yielding different isoforms resulting from alternative splicing (Himmler, 1989; Andreadis, 2005) or intron retention (Garcia-Escudero et al., 2021). The expression of the different tau isoforms may depend on different genetic factors. For example, there are two main different haplotypes (Caffrey and Wade-Martins, 2007; Santa-Maria et al., 2012) for *mapt* gene, the one that express Tau protein. Also, the post-transcriptional expression of Tau may be regulated by factors like micro-RNA-219 (Santa-Maria et al., 2015). The translated Tau protein isoforms are internally disorder proteins (IDP) (Skrabana et al., 2006), although a conformation (‘‘paper-clip” conformation), involving the interaction of N and C terminal ends, has been reported (Jeganathan et al., 2006). Also, a structural stabilization could occur after binding to microtubules or tau self-aggregation (Zhang et al., 2019; Shi et al., 2021).

In addition to its role as cytoskeletal protein (Avila et al., 2004), Tau protein has other functions. For example, there is a role of Tau in long term depression (Kimura et al., 2014), in stress-induced brain pathology (Lopes et al., 2016), in the function of extrasynaptic NMDA receptors (Pallas-Bazarra et al., 2019) or in regulating the effects of external stimuli on adult hippocampal neurogenesis (Pallas-Bazarra et al., 2016), among other ones.

However, we are focusing our work, in this Special Issue, on the role of Tau in some neurodegenerative disorders known as tauopathies. The role of Tau in other health problems (like chronic pain, see Guerreiro et al., 2022) will not be commented.

Tauopathies are neurodegenerative disorders characterized by the presence of tau aggregates in brain (Avila et al., 2016; Goedert and Spillantini, 2019; Zhang et al., 2022). Over twenty different types of tauopathies have been described (Fernandez-Nogales et al., 2014; Sexton et al., 2022), being the most prevalent one, Alzheimer disease (Grundke-Iqbal et al., 1986; Kosik et al., 1986; Lee et al., 2001; Liu and Gong, 2008), in which a decreased turnover of the protein facilitates its accumulation, its post-translational modifications and aggregation into toxic polymers.

In this Special Issue some different points related to tauopathies will be commented. These points are linked to:

1. The role of *mapt* gene (and other associated genes) in different tauopathies. In addition to the nuclear genome, the effect of other genes (microbiome) on neurodegeneration will be discussed.
2. The different roles of different Tau isoforms in different tauopathies where toxic Tau could be present in different cells types and different subcellular localization will be commented.
3. The interaction of Tau with macromolecules structures that could facilitate neurodegeneration will be described.
4. Some types of posttranscriptional modifications related to neurodegeneration will be shown.
5. The role of glia cells in neurodegenerative disorders, like Alzheimer’s disease will be indicated.
6. Tau protein conformational changes resulting in aggregation and neurodegeneration will be quoted.

7. Finally, a commentary on the possible Tau clearance to regulate Tau proteostasis to avoid aggregation is included.

In the first point, Gallo et al. (2022) have described the role of *mapt* gene with or without familial mutations in some tauopathies like Pick's disease (PiD), progressive supranuclear palsy (PSP), cortical basal degenerations (CBD), argyrophilic grain disease (AGD) or primary age-related tauopathy (PART). In the case of PSP or CBD, the presence of H1 haplotype could favor the development of the disorder. In other contribution Moreno-Arribas (Molinero et al., 2023) and collaborators have described the role of other genes, unrelated to nuclear genes, present in the microbiome in human neurodegenerative disorders.

In the second point, the relation of different tau isoforms with different tauopathies is indicated in the work of several French-speaking groups (Petry et al., 2022), related to the different regulation of Tau exon 2 and 10 isoforms in Huntington's disease. Also, different Tau isoforms could have different subcellular localization and Hernañdez and colleagues (Anton-Fernandez et al., 2022) have focused on those related to the presence of Tau in the cell nucleus.

In the third point, Jimenez (2022) has reviewed the interaction of Tau with macromolecules structures, including some thermodynamic data for a quantitation of the interaction. In addition, Berrocal and Mata (2022) have described the link between Tau and the plasma membrane Ca^{2+} pump. This link could alter the regulations of intracellular calcium, promoting neurodegeneration.

The fourth point is related to posttranslational modifications of Tau, related to Tau pathology. Six different groups coordinated by Ferrer (Andres-Benito et al., 2021) have described the components of cytoplasmic granules present in granuvascular degeneration found at early stages of neurofibrillary tangle pathology. Curiously, other brain microtubule associated proteins like MAP2 or MAP1B in phosphorylated form, are some of those components, in addition to P-Tau. In other article, Arnal (Fourest-Lieuvin et al., 2022) and collaborators described how controlled tau cleavage may result in an abnormal localization of the resulting cleaved tau fragments.

The fifth point shows the role of different types of glia cells in neurodegeneration, indicating, by Caamano-Moreno and Gargini (2022), the role of Tau in cellular crosstalk and synaptic dysfunction. In addition, Hargus and collaborators (Qu et al., 2022) have summarized the function of neurons, microglia and astrocytes in the pathogenesis of Alzheimer's disease and, also support the significance of human induced pluripotent stem cells (iPSCs) in modeling disease development.

The sixth point focus on tau conformational changes that facilitate its aggregation that will result in neurodegeneration. Garcia-Sierra and collaborators (Horta-Lopez et al., 2022) have described the association between the expression of alpha1-antichymotrypsin with Tau conformational changes that facilitate Tau aggregation in Alzheimer's disease brain. In other work, Frost and collaborators (Schulz et al., 2022), using a Drosophila model of tauopathy, found that the increase of activity-regulated cytoskeleton associated protein (Arc1), induced by Tau protein, is a factor contributing to neuronal death. In a third work, Avila and collaborators (Hernandez et al., 2022) have revised the aggregation of Tau looking at different structural levels like the primary, secondary, tertiary and quaternary structures of monomeric and aggregated Tau.

Finally, as a commentary, Johnson and collaborators (Lin et al., 2022) indicate that Tau clearance, to avoid its aggregation and toxicity, can be carried out through BLC2 associated athanogene 3 (BAG3), a multidomain protein that has an important role in maintaining neuronal proteostasis.

In summary, we are thankful to all the contributors for making possible the publication of this Special Issue on tauopathies, a field that, we hope, will provide in the future, important answers for the treatment of neurological disorders.

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