



NDUFA12L mitochondrial complex-I assembly factor: Implications for taupathies



Mohamed Salama^a, Wael M.Y. Mohamed^{b,*}

^a Toxicology Department, Mansoura University, Egypt

^b Clinical Pharmacology Dept, Menoufia Medical School, Menoufia University, Egypt

ARTICLE INFO

Article history:

Received 19 May 2015

Accepted 29 May 2015

Keywords:

Taupathies

Mitochondrial complex

Neurodegeneration

ABSTRACT

There is a strong correlation between taupathies and the development and progression of neurodegenerative disorders. Abnormal tau becomes hyperphosphorylated and dissociated from microtubules with the aggregation of intracellular tau aggregates within the patient's brain. The current review is divided into two broad sections. In the first section we discuss the molecular biology and the clinicopathologic features of taupathies. While in the second section we discuss the relationship between mitochondrial complex-I and taupathies. Polymorphism in NDUFA12L may be a crucial factor for development of neurodegenerative taupathies. Thus NDUFA12L screening may be an early biomarker for identifying risk groups for such disorders.

© 2015 Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Contents

1. Introduction	37
1.1. Molecular biology of taupathies	37
2. Clinico-pathologic patterns of taupathies	38
2.1. Mitochondrial complex-I and taupathies	38
3. Conclusions and future directions	39
References	39

1. Introduction

The elderly population is living longer and increasingly struck by neurodegenerative disorders. Therefore, studying these disorders is increasingly imperative (Denk and Wade-Martins, 2009) particularly, taupathies (Ludolph et al., 2009). Advances in histo-pathological techniques improved our understanding of many neurodegenerative disorders via characterization of the insoluble proteins in neuronal and glial cells, and taupathies are no exclusion (Goedert, 2004). Tau is a Micro-tubular Associated Protein (MAP) in the brain. It was assigned a Greek letter “T” to indicate its ability to assemble tubulin (Weingarten et al., 1975). It maintains the neural function and transport of signals through axons and dendrites of neurons (Kovacs, 2015), and plays an important role in micro-tubular function as it binds to microtubules leading to their assembly and stabilization (Spillantini and Goedert, 2013). Soluble tau may undergo posttranslational modifications as hyper phosphorylation and convert to insoluble neurofibrillary tau

(NFT). Hence, in taupathies, the soluble tau protein disengages from the microtubules and forms odd aggregates of tau, which is ubiquitinated (Kumar Dasappa and Nagendra, 2013; Shiryayev et al., 2009). There are six isoforms of tau protein expressed by the Micro-tubular Associated Protein Tau (MAPT) gene located on chromosome 17, so any mutations in the MAPT gene are associated with fronto-temporal dementia and Parkinsonism linked to chromosome 17 (FTDP-17MAPT) (Kovacs, 2015). Thus, taupathy is increasingly recognized as a possible contributing factor in the development of Parkinson's disease (PD) (Spillantini and Goedert, 2013).

1.1. Molecular biology of taupathies

In normal brains, tau is thought to have important roles in microtubule stabilization and assembly. Moreover, tau may help in signal transduction mechanisms, interactions with the actin cytoskeleton, neurite outgrowth and stabilization during brain development (Binder et al., 1985; Kambe et al., 2011). Tau is alternatively spliced in exons 2, 3, and 10, forming six different tau isoforms. Exon 10 splice products are particularly prone to mutations, which may affect the aggregation of

* Corresponding author.

E-mail address: wmy107@gmail.com (W.M.Y. Mohamed).

tau, forming three isoforms with three microtubule-binding repeats (3R tau) and three isoforms with four microtubule-binding repeats (4R tau). While NFTs have historically been considered the main hallmark in tauopathies, they do not appear to be the main toxic species in disease. Cell death occurs in disease prior to the formation of NFTs (van de Nes et al., 2008; Gerson et al., 2014) and NFT-containing neurons have been shown to be functionally intact in vivo (Kuchibhotla et al., 2014). Tau animal models show all the criteria of the disease i.e. behavioral disturbance and locomotor deterioration without NFT formation (Cowan et al., 2010). It seems that tau oligomers (the intermediate tau species that form between tau monomers and NFTs) are responsible for the onset of disease. Tau oligomer levels have been correlated to the clinical symptoms in Alzheimer's disease (AD) and Progressive Supra-nuclear Palsy (PSP) brains (Gerson et al., 2014). Additionally, when administering tau oligomers to wild-type mice, synaptic and mitochondrial dysfunction as well as cognitive deficits have been observed (Lasagna-Reeves et al., 2011). The disordered, high energy state of monomeric tau, when released from binding to microtubules, allows for the exposure of hydrophobic patches and the formation of intermolecular contacts, leading to the mis-folding and aggregation of the tau monomer in disease. Tau fibrils that comprise NFTs are composed of hyperphosphorylated tau in cross β -sheet conformation common to amyloid fibrils (von Bergen et al., 2005) and take on two major forms: paired helical filaments (PHFs) and straight filaments. Tau fibrils are capable of seeding the fibrillization of the tau monomer by template-assisted growth, whereby monomers that come into contact with the tau filament are integrated into parallel β -sheet structure (Barghorn and Mandelkow, 2002; Chirita et al., 2003). Tau oligomers have been further shown to be the precursors for tau aggregation, through a process called oligomer-nucleated conformational induction (Lee et al., 2011) in which the tau monomer is first converted to an oligomeric state then fibrils are formed. Post-translational modifications and the formation of disulfide bridges increase the ability of tau to form oligomers (Sahara et al., 2007). Furthermore, tau oligomers were detected in AD patients' platelets, suggesting that such tau could serve as a new biological marker for AD (Neumann et al., 2011).

2. Clinico-pathologic patterns of tauopathies

Tauopathies are the etiological name for certain disorders that share the same abnormal tau aggregates. Tauopathies include nearly more than 20 different degenerative disorders especially Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD) (Kovacs, 2015; Spillantini and Goedert, 2013; Xie et al., 2014). All these disorders contain insoluble tau inclusions with cell injury and death (Williams, 2006). FTLD includes frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17), Pick's disease (PiD), argyrophilic grain dementia (AGD), progressive supra-nuclear palsy (PSP), and corticobasal degeneration (CBD) (Takenokuchi et al., 2010). Furthermore, Parkinson's disease (PD) which is the most frequent cause of Parkinsonism, is known as α -synucleinopathies as it shows many Lewy bodies with multiple tau antibodies (Skovronsky, 2007). Tau is found as aggregated abnormal filaments, such as neurofibrillary tangles within the brains of tauopathic patients. These insoluble tau portions are localized in the somatodendritic compartments of cells, in contrast to their usual localization in axons. Tangles have different distributions and ultrastructural morphologies in the brain according to specific tauopathies and specific disease-causing mutations. For instance, AD neurofibrillary tangles consist of paired helical filaments. Patients with PSP and FTDP-17 and mutations in exon 10 have neurofibrillary tangles with straight tau filaments (Kambe et al., 2011). Unfortunately, there is no currently available treatment to improve the prognosis of any of these progressive diseases. Consequently, researchers are aiming at determination of the underlying pathophysiology of tauopathies, in order to isolate novel therapeutic agents that prevent disease progression (Ludolph et al., 2009). It is noteworthy that accumulation of tau

oligomers results in mitochondrial dysfunction with learning and memory impairment (Huang et al., 2006; Zhang et al., 2006).

2.1. Mitochondrial complex-I and tauopathies

Mitochondrial dysfunction is thought to play an important role in the development of tau pathology (Kulic et al., 2009). Mitochondrial complex-I is a group of eukaryotic intracellular organelles, which utilize the cells' energy. Inside the mitochondria, the oxidative phosphorylation (OXPHOS) pathway harvests the energy into nutrients and transforms it into adenosine triphosphate (ATP) (Wanrooij and Falkenberg, 2010). Hence, mitochondrial dysfunction leads to impairment in energy metabolism and oxidative stress, effects that are linked to aging processes and many age-related neurodegenerative conditions (Gibson et al., 2010). The OXPHOS system, which is embedded in the lipid bilayer of the mitochondrial inner membrane, is the final biochemical pathway in the energy production of the cell (Janssen et al., 2004). This system consists of five enzyme complexes with two mobile electron carriers. NADH: Ubiquinone oxidoreductase (complex I) the first and the largest of the five complexes is one of the two entry points of the OXPHOS system (complex II being the other). It initiates electron transfer by oxidizing NADH and using the lipid soluble ubiquinone as the electron acceptor (Valsecchi et al., 2009). Complex I (CI) consists of 45 different subunits; seven of them are encoded by the mitochondrial DNA (mtDNA), while the nuclear DNA (nDNA) encodes the remainder. In addition, proper assembly of functional CI requires the assistance of what is called assembly factors. These are several proteins that are involved in the assembly of CI but are not part of the final structure of the enzyme. Identification of these assembly factors opens a new field of possible pathways leading to CI deficiency (Willems et al., 2009). NDUFA12L appears to be important for the correct assembly and function of a multi-protein complex implicated in the energy production of cells. Presently, the biological consequences of NDUFA12L deletions are not known. At least 6 factors (NDUFA1/CIA30, NDUFAF2/NDUFA12L/B17.2L/Mimetin, C6orf66/HRPAP20, C8orf38, C20orf7 and Ecsit) have been identified so far. Mutations in assembly factors reduce the amount of fully assembled functional complex by affecting the rate of CI stability. A mutation in exon 2 of the gene encoding NDUFA12L resulting in a premature stop codon was identified in a patient with progressive encephalopathy. The patient presented with severe enzymatic deficiency of complex I that also correlated with reduced assembly of the enzyme. Furthermore, given that NDUFA12L was shown to associate with complex I subunits ND1, NDUFS1, NDUFS2 and NDUFS7 and Cure PSP Genetics Consortium has now found an abnormal heterozygous absence (deletion) of the gene NDUFA12L in association with individual patients with PSP, which represents one of the major tauopathy publications in preparation. NDUFS4 in normal mitochondria, it seems to play a direct role in CI assembly (Lazarou et al., 2009). In another study, in two clinical cases with mutation in the same assembly factor, NDUFA12L, the activity of CI was reduced. This was accompanied by involvement of the mamillothalamic tracts, substantia nigra/medial lemniscus, medial longitudinal fasciculus, the corpus medullare and the cerebellum (Barghuti et al., 2008). Detailed knowledge of the cytopathological consequences of CI deficiency is prerequisite to understanding the clinical presentations and their heterogeneity, and developing therapeutic strategies (Distelmaier et al., 2009). There are epidemiological (Lannuzel et al., 2007), biochemical (Albers et al., 2000, 2001; Swerdlow et al., 2000), MR-spectroscopical (Stamelou et al., 2009), experimental (Hoglinger et al., 2005; Escobar-Khondiker et al., 2007; Höllerhage et al., 2009), and clinical (Stamelou et al., 2008) evidence suggesting that CI dysfunction might be functionally involved in the pathogenesis of the tauopathy PSP. Particularly, previous data showed that accumulation of hyperphosphorylated tau occurs in the somatodendritic compartment in neurons after administration of neurotoxins, acting as CI inhibitors (Escobar-Khondiker et al., 2007; Höllerhage et al., 2009). Thus, a potential functional impact of mutations

in the gene encoding the NDUFA12L assembly factor on the pathogenesis of tauopathies seems an attractive hypothesis that needs to be tested. However, at present, no data about the biochemical, pathological or clinical consequence of NDUFA12L deletions are available.

3. Conclusions and future directions

There is no doubt that tau oligomers and tauopathies are becoming an extremely important endeavor in neurodegenerative disease research. Thus, a better understanding of the deleterious effects of tau oligomers on the brain with a focus on the mitochondrial complex, will likely be of great importance to solve the mystery of the underlying pathology of neurodegenerative disorders and other tauopathies. As can be seen, NDUFA12L has an important role for homeostasis of CI, thus affecting OXPHOS and mitochondria, which play a critical role in neurodegenerative disorder pathogenesis. Based on that, polymorphism in this assembly factor may pose a risk for developing such disorders. In brief, screening for NDUFA12L dysfunction may identify risk group for neurodegeneration with further opportunity of early intervention. Transgenic models are available to test and validate the aforementioned link, which may accelerate the discovery of more effective therapies for neurodegenerative tauopathies and related disorders.

References

- Albers, D.S., Augood, S.J., Park, L.C., et al., 2000. Frontal lobe dysfunction in PSP: evidence for oxidative stress and mitochondrial impairment. *J. Neurochem.* 74, 878–881.
- Albers, D.S., Swerdlow, R.H., Manfredi, G., et al., 2001. Further evidence for mitochondrial dysfunction in progressive supranuclear palsy. *Exp. Neurol.* 168, 196–198.
- Barghorn, S., Mandelkow, E., 2002. Toward a unified scheme for the aggregation of tau into Alzheimer paired helical filaments. *Biochemistry* 41, 14885–14896.
- Barghuti, F., Elian, K., Gomori, J.M., et al., 2008. The unique neuroradiology of complex I deficiency due to NDUFA12L defect. *Mol. Genet. Metab.* 94, 78–82.
- Binder, L.I., Frankfurter, A., Rebhun, L.L., 1985. The distribution of tau in the mammalian central nervous system. *J. Cell Biol.* 101, 1371–1378.
- Chirita, C.N., Necula, M., Kuret, J., 2003. Anionic micelles and vesicles induce tau fibrillization in vitro. *J. Biol. Chem.* 278, 25644–25650.
- Cowan, C.M., Bossing, T., Page, A., Shepherd, D., Mudher, A., 2010. Soluble hyperphosphorylated tau causes microtubule breakdown and functionally compromises normal tau in vivo. *Acta Neuropathol.* 120, 593–604.
- Denk, F., Wade-Martins, R., 2009. Knock-out and transgenic mouse models of tauopathies. *Neurobiol. Aging* 30 (1), 1–13.
- Distelmaier, F., Visch, H.-J., Smeitink, J., et al., 2009. The antioxidant Trolox restores mitochondrial membrane potential and Ca^{2+} -stimulated ATP production in human complex I deficiency. *J. Mol. Med.* 87, 515–522.
- Escobar-Khondiker, M., Höllerhage, M., Muriel, M., et al., 2007. Annonacin, a natural mitochondrial complex I inhibitor, causes tau pathology in cultured neurons. *J. Neurosci.* 27, 7827–7837.
- Gerson, J.E., Castillo-Carranza, D.L., Kaye, R., 2014. Advances in therapeutics for neurodegenerative tauopathies: moving toward the specific targeting of the most toxic tau species. *ACS Chem. Neurosci.* 5 (9), 752–769.
- Gibson, G.E., Starkov, A., Blass, J.P., et al., 2010. Cause and consequence: mitochondrial dysfunction initiates and propagates neuronal dysfunction, neuronal death and behavioral abnormalities in age-associated neurodegenerative diseases. *Biochim. Biophys. Acta* 1802, 122–134.
- Goedert, M., 2004. Tau protein and neurodegeneration. *Semin. Cell Dev. Biol.* 15, 45–49.
- Hoglinger, G.U., Lannuzel, A., Khondiker, M.E., et al., 2005. The mitochondrial complex I inhibitor rotenone triggers a cerebral tauopathy. *J. Neurochem.* 95, 930–939.
- Höllerhage, M., Matusch, A., Champy, P., et al., 2009. Natural lipophilic inhibitors of mitochondrial complex I are candidate toxins for sporadic neurodegenerative tau pathologies. *Exp. Neurol.* 220, 133–142.
- Huang, S.M., Mouri, A., Kokubo, H., Nakajima, R., Suemoto, T., Higuchi, M., Staufenbiel, M., Noda, Y., Yamaguchi, H., Nabeshima, T., Saido, T.C., Iwata, N., 2006. Neprilysin-sensitive synapse-associated amyloid-beta peptide oligomers impair neuronal plasticity and cognitive function. *J. Biol. Chem.* 281, 17941–17951.
- Janssen, R.J., van del Heuvel, L.P., Smeitink, J., 2004. Genetic defects in oxidative phosphorylation (OXPHOS) system. *Expert. Rev. Mol. Diagn.* 4 (2), 143–156.
- Kambe, T., Motoi, Y., Inoue, R., et al., 2011. Differential regional distribution of phosphorylated tau and synapse loss in the nucleus accumbens in tauopathy model mice. *Neurobiol. Dis.* <http://dx.doi.org/10.1016/j.nbd.2011.02.002>.
- Kovacs, G., 2015. Invited review: neuropathology of tauopathies: principles and practice. *Neuropathol. Appl. Neurobiol.* 41 (1), 3–23.
- Kuchibhotla, K.V., Wegmann, S., Kopeikina, K.J., Hawkes, J., Rudinskiy, N., Andermann, M.L., Spire-Jones, T.L., Bacskai, B.J., Hyman, B.T., 2014. Neurofibrillary tangle-bearing neurons are functionally integrated in cortical circuits in vivo. *Proc. Natl. Acad. Sci. U. S. A.* 111, 510–514.
- Kulic, L., Wollmer, M.A., Rhein, V., et al., 2009. Combined expression of tau and the Harlequin mouse mutation leads to increased mitochondrial dysfunction, tau pathology and neurodegeneration. *Neurobiol. Aging* <http://dx.doi.org/10.1016/j.neurobiolaging.2009.10.014>.
- Kumar Dasappa, J., Nagendra, H., 2013. Preferential selectivity of inhibitors with human tau protein kinase Gsk3 elucidates their potential roles for off-target Alzheimer's therapy. *Int. J. Alzheimers Dis.* 2013, 1–8. <http://dx.doi.org/10.1155/2013/809386>.
- Lannuzel, A., Höglinger, G.U., Verhaeghe, S., et al., 2007. Atypical parkinsonism in Guadeloupe: a common risk factor for two closely related phenotypes? *Brain* 130, 816–827.
- Lasagna-Reeves, C.A., Castillo-Carranza, D.L., Sengupta, U., Clos, A.L., Jackson, G.R., Kaye, R., 2011. Tau oligomers impair memory and induce synaptic and mitochondrial dysfunction in wild-type mice. *Mol. Neurodegener.* 6 (39). <http://dx.doi.org/10.1186/1750-1326-6-39> (6).
- Lazarou, M., Thorburn, D.R., Ryan, M., et al., 2009. Assembly of mitochondrial complex I and defects in disease. *Biochim. Biophys. Acta* 1793, 78–88.
- Lee, J., Culyba, E.K., Powers, E.T., Kelly, J.W., 2011. Amyloid-beta forms fibrils by nucleated conformational conversion of oligomers. *Nat. Chem. Biol.* 7, 602–609.
- Ludolph, A.C., Kassubek, J., Landwehrmeyer, B.G., et al., 2009. Tauopathies with parkinsonism: clinical spectrum, neuropathologic basis, biological markers, and treatment options. *Eur. J. Neurol.* 16 (3), 297–309.
- Neumann, K., Farias, G., Slachevsky, A., Perez, P., Maccioni, R.B., 2011. Human platelets tau: a potential peripheral marker for Alzheimer's disease. *J. Alzheimers Dis.* 25, 103–109. <http://dx.doi.org/10.3233/JAD-2011-101641>.
- Sahara, N., Maeda, S., Murayama, M., Suzuki, T., Dohmae, N., Yen, S.-H., Takashima, A., 2007. Assembly of two distinct dimers and higher-order oligomers from full-length tau. *Eur. J. Neurosci.* 25, 3020–3029.
- Shiryayev, N., Jouroukhin, Y., Giladi, E., et al., 2009. NAP protects memory, increases soluble tau and reduces tau hyperphosphorylation in a tauopathy model. *Neurobiol. Dis.* 34, 381–388.
- Skovronsky, D.M., 2007. Tau in Parkinsonian Diseases. In: Dawson, T.M. (Ed.), *Parkinson's Disease Genetics and Pathogenesis*. Informa Healthcare, New York, London, pp. 187–198.
- Spillantini, M., Goedert, M., 2013. Tau pathology and neurodegeneration. *Lancet Neurol.* 12 (6), 609–622. [http://dx.doi.org/10.1016/s1474-4422\(13\)70090-5](http://dx.doi.org/10.1016/s1474-4422(13)70090-5).
- Stamelou, M., Reuss, A., Pilatus, U., et al., 2008. Short-term effects of coenzyme Q10 in progressive supranuclear palsy: a randomized, placebo-controlled trial. *Mov. Disord.* 23, 942–949.
- Stamelou, M., Pilatus, U., Reuss, A., et al., 2009. In vivo evidence for cerebral depletion in high-energy phosphates in progressive supranuclear palsy. *J. Cereb. Blood Flow Metab.* 29, 861–870.
- Swerdlow, R.H., Golbe, L.I., Parks, J.K., et al., 2000. Mitochondrial dysfunction in cybrid lines expressing mitochondrial genes from patients with progressive supranuclear palsy. *J. Neurochem.* 75, 1681–1684.
- Takenokuchi, M., Kadoyama, K., Chiba, S., et al., 2010. SJLB mice develop tauopathy-induced parkinsonism. *Neurosci. Lett.* 473, 182–185.
- Valsecchi, F., Esseling, J.J., Koopman, W., et al., 2009. Calcium and ATP handling in human NADH:ubiquinone oxidoreductase deficiency. *Biochim. Biophys. Acta Mol. Basis Dis.* <http://dx.doi.org/10.1016/j.bbdis.2009.01.001>.
- van de Nes, J.A., Nafe, R., Schlote, W., 2008. Non-tau based neuronal degeneration in Alzheimer's disease: an immunocytochemical and quantitative study in the supragranular layers of the middle temporal neocortex. *Brain Res.* 1213, 152–165.
- von Bergen, M., Barghorn, S., Biernat, J., Mandelkow, E.-M., Mandelkow, E., 2005. Tau aggregation is driven by a transition from random coil to beta sheet structure. *Biochim. Biophys. Acta Mol. Basis Dis.* 1739, 158–166.
- Wanrooij, S., Falkenberg, M., 2010. The human mitochondrial replication fork in health and disease. *Biochim. Biophys. Acta* 1797, 1378–1388.
- Weingarten, M.D., Lockwood, A.H., Hwo, S.Y., Kirschner, M.W., 1975. A protein factor essential for microtubule assembly. *Proc. Natl. Acad. Sci. U. S. A.* 72, 1858–1862.
- Willems, P., Smeitink, J., Koopman, W., 2009. Mitochondrial dynamics in human NADH: ubiquinone oxidoreductase deficiency. *Int. J. Biochem. Cell Biol.* 41, 1773–1782.
- Williams, D.R., 2006. Tauopathies: classification and clinical update on neurodegenerative diseases associated with microtubule-associated protein tau. *Intern. Med. J.* 36, 652–660.
- Xie, A., Gao, J., Xu, L., Meng, D., 2014. Shared mechanisms of neurodegeneration in Alzheimer's disease and Parkinson's disease. *Biomed Res. Int.* 2014, 1–8. <http://dx.doi.org/10.1155/2014/648740>.
- Zhang, L., Xing, Y., Ye, C.F., Ai, H.X., Wei, H.F., Li, L., 2006. Learning-memory deficit with aging in APP transgenic mice of Alzheimer's disease and intervention by using tetrahydroxystilbene glucoside. *Behav. Brain Res.* 173, 246–254.