ACS Chemical Neuroscience
Cite This: ACS Chem. Neurosci. 2019, 10, 1133−1134
Viewpoint
pubs.acs.org/chemneuro

Abnormal Microtubule Dynamics Impair the Nuclear-Cytoplasmic Transport in Dementia

Timir Tripathi* and Jupitara Kalita

Molecular and Structural Biophysics Laboratory, Department of Biochemistry, North-Eastern Hill University, Umshing, Shillong 793022, Meghalaya, India

ABSTRACT: Disrupted nuclear-cytoplasmic transport (NCT) is a common pathophysiological event in several neurodegenerative disorders. However, the correlation between the mutations in the pathogenic microtubule-associated protein tau and NCT and neuronal dysfunction is not yet clearly understood. A recent study revealed that tau is mislocalized to the neuronal cell body and, thus, deforms the nuclear membrane in the frontotemporal dementia (FTD). This causes a defect in NCT, leading to neurodegeneration. The microtubule depolymerization could rescue the NCT defects as well as neurodegeneration. Therefore, agents that can modulate the microtubule functions or NCT can constitute a potential therapeutic method for the treatment of neurodegenerative disorders.

KEYWORDS: *Microtubule, mislocalization, hyperphosphorylated tau, microtubule-associated protein tau, aggregation, nuclear lamina, nuclear membrane, nuclear-cytoplasmic transport, neurodegeneration, frontotemporal dementia*

Downloaded via 65.21.193.86 on February 24, 2022 at 17:01:03 (UTC).
See https://pubs.acs.org/sharingguidelines for options on how to legitimately share published articles.

The aggregation of hyperphosphorylated tau (P-tau) is involved in the pathogenesis of diverse forms of neurodegenerative disorders, including Alzheimer's disease and frontotemporal dementia (FTD).[1] P-tau is associated with the neuronal microtubules. The missense and splicing mutations in tau are related to the familial FTD.[2] However, the mechanism underlying the mutations in tau that are responsible for FTD is yet unknown. Interestingly, tau has been demonstrated to mislocalize to the cell bodies and dendrites in the neocortex. Consequently, the microtubules display abnormal movements, which in turn results in deformed nuclear membrane and, thus, defective nuclear-cytoplasmic transport (NCT). The inhibition of the polymerization of microtubules decreases the neurodegeneration by suppressing the NCT defect in FTD.[3] Since the defects in the NCT have been identified as a critical event in the pathogenesis of several neurodegenerative disorders,[4] the neuronal dysfunction represents a convergence among abnormal microtubule dynamics, nuclear membrane dysfunction, and NCT. The current data rendered the dysfunction of the nuclear membrane as a common pathogenic mechanism underlying several neurodegenerative disorders. Thus, this defect could be targeted by agents that regulate the microtubule functions, NCT, and/or the associated processes for therapeutic purposes (Figure 1).

The tau protein is localized exclusively in the axon of the normal neurons, while in tau-mediated dementia, it is mislocalized and aggregated in the neuronal cell bodies. Strikingly, this mislocalization is a key event in the early onset FTD.[5] The aggregation of P-tau is the hallmark of neurodegeneration and specifically affects the autophagy and proteostasis in neurons. Nevertheless, the mechanism due to which the tau mutations drive the hyperphosphorylation and mislocalization of tau and the resulting effects on neurons that lead to neuronal dysfunction are yet to be elucidated. In order to understand the effects of tau mutations, the authors generated human induced pluripotent stem cells (iPSCs)-derived cortical neurons from persons with two different classes of tau mutations (missense and splicing) that caused FTD. The results demonstrated that the total tau content was almost comparable in both genotypes of neurons (together denoted as FTD-tau neurons), while the phosphorylation of the protein was increased in FTD-tau neurons in comparison with the controls. Moreover, both mutations were found to cause mislocalization of tau into the cell bodies and dendrites of the FTD-tau neurons. The tau of FTD-tau neurons was hyperphosphorylated. Interestingly, the microtubule dynamics

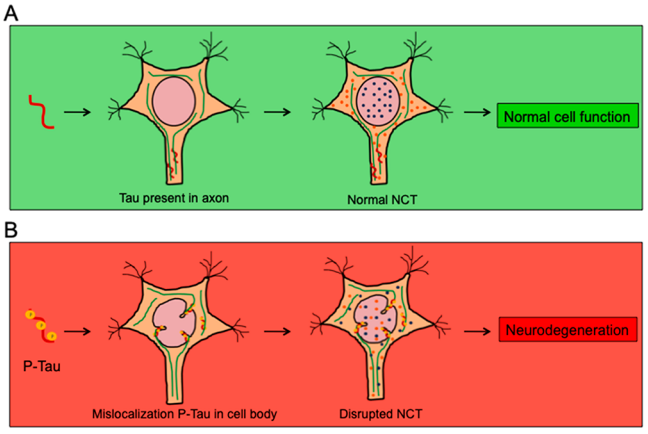

Figure 1. Schematic representation of the effect of tau on nuclear membrane and NCT of FTD-tau neurons. (A) Normal NCT occurs when P-tau is present in the axons of normal neurons. (B) Impaired NCT occurs when P-tau is mislocalized to the cell body of FTD-tau neurons, due to which, the microtubules invaginate the nuclear membrane that is disrupted in NCT.

Received: February 4, 2019
Accepted: February 5, 2019
Published: February 20, 2019

 © 2019 American Chemical Society
DOI: 10.1021/acschemneuro.9b00079
ACS Chem. Neurosci. 2019, 10, 1133−1134

were also altered. The control neurons consisted of several actively growing microtubules within the cell body, while those of FTD-tau neurons abnormally projected into the neuronal nucleus. Next, the authors examined the morphology of the nuclear membrane in iPSC-derived neurons and observed large invaginations of the lamin B1-positive inner nuclear lamina within the nucleus of the FTD-tau neurons. Thus, the microtubules were found to actively distort the nuclear membrane of the FTD-tau neurons. Furthermore, the microtubule depolymerization considerably decreased the percentage of neurons with nuclear lamina invaginations and reinstated the nuclear architecture. Thus, it could be concluded that the deformations of the neuronal nuclear membrane in FTD-tau neurons are effectuated by abnormal microtubule dynamics. Subsequently, the super-resolution imaging of the nucleus in iPSC-derived neurons was performed to understand the spatial associations among tau, microtubules, and the nuclear membrane. The results demonstrated a close association between tau and tubulin within the nuclear invaginations of the nuclear membrane in FTD-tau neurons. The next question was whether the alterations in the nuclear membrane are also characteristics of FTD-tau in vivo. To address this question, the authors examined the nuclear invaginations in the frontal and temporal cortex from two independent cohorts, both comprising of individuals with FTD due to tau mutations and compared each to that in the nondemented controls. The fraction of all nuclei with invaginations within each region of the brain was quantified. The data suggested that lamin B1-positive nuclear invaginations were associated with the presence of P-tau within the neuronal cell body and that the nuclear lamina was completely disrupted in the neurons with high levels of P-tau. Finally, since alterations in the nuclear membrane lead to destructive effects on nuclear function, the effect on the NCT in FTD-tau neurons also needed further exploration. To address this concern, NES:GFP (nuclear export signal fused to green fluorescent protein) and NLS:RFP (nuclear localization signal fused to red fluorescent protein) were expressed from a single construct in iPSC-derived neurons. The control neurons presented distinct cellular distributions of each protein with prominent nuclear RFP and cytosolic GFP, while the localization of NLS:RFP was altered in FTD-tau neurons due to a marked decrease in the nuclear/cytoplasmic RFP ratio. Together, these results revealed an overall NCT failure within the FTD-tau neurons. The microtubule depolymerization restored the distribution of both NES:GFP and NLS:RFP in FTD-tau neurons to healthy levels, thereby indicating that the defective NCT in FTD-tau neurons is a continuous activity attributed to the microtubule-mediated nuclear membrane deformation.

Nevertheless, the mechanism underlying the pathogenesis of FTD due to tau mutations is yet to be elucidated. It can be speculated that tau mutations lead to P-tau aggregation, which is the initial trigger of neurodegeneration. The present study demonstrated that P-tau mislocalizes to and becomes a part of the neuronal cell body, resulting in impaired NCT. Moreover, the disruption of the nuclear lamina leads to dysfunctional nuclear membrane and impaired NCT in FTD-tau neurons, and that of the nuclear lamina is attributed to altered microtubule dynamics. Together, these data suggested that the perturbed function of the nuclear membrane and disrupted NCT are critical pathogenic processes in dementias involving protein aggregation. Thus, for the treatment of neurodegenerative disorders related to impaired NCT, neurotherapeutics that can target and regulate the microtubule functions, NCT, and/or associated processes should be developed.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: timir.tripathi@gmail.com.

ORCID

Timir Tripathi: 0000-0001-5559-289X

Funding

The work was partly supported by a Department of Biotechnology grant, India (Grant No. MED/2017/50).

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Paonessa, F., et al. (2019) Microtubules Deform the Nuclear Membrane and Disrupt Nucleocytoplasmic Transport in Tau-Mediated Frontotemporal Dementia. *Cell Rep. 26*, 582−593.

(2) Spillantini, M. G., and Goedert, M. (2013) Tau pathology and neurodegeneration. *Lancet Neurol. 12*, 609−622.

(3) D'Souza, I., Poorkaj, P., Hong, M., Nochlin, D., Lee, V. M., Bird, T. D., and Schellenberg, G. D. (1999) Missense and silent tau gene mutations cause frontotemporal dementia with parkinsonism-chromosome 17 type, by affecting multiple alternative RNA splicing regulatory elements. *Proc. Natl. Acad. Sci. U. S. A. 96*, 5598−5603.

(4) Tripathi, T., Prakash, J., and Shav-Tal, Y. (2019) Phospho-Tau impairs nuclear-cytoplasmic transport. *ACS Chem. Neurosci. 10*, 36−38.

(5) Caballero, B., Wang, Y., Diaz, A., Tasset, I., Juste, Y. R., Stiller, B., Mandelkow, E.-M., Mandelkow, E., and Cuervo, A. M. (2018) Interplay of pathogenic forms of human tau with different autophagic pathways. *Aging Cell 17*, No. e12692.

DOI: 10.1021/acschemneuro.9b00079
ACS Chem. Neurosci. 2019, 10, 1133−1134