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Why Microtubules Should Be Considered as One of the Supplementary Targets for Designing Neurotherapeutics

Gaurav Das and Surajit Ghosh*

Organic & Medicinal Chemistry Division, CSIR-Indian Institute of Chemical Biology, 4 Raja S. C. Mullick Road, Jadavpur, Kolkata-700032, West Bengal India

Academy of Scientific and Innovative Research (AcSIR), CSIR-Indian Institute of Chemical Biology Campus, 4 Raja S. C. Mullick Road, Kolkata 700 032, India

ABSTRACT: In the past decade of research, drugs targeting amyloid beta (Aβ) have failed in clinical amelioration of Alzheimer's disease (AD). This has led to researchers searching for more attractive targets. Here, we discuss one such approach of developing future neurotherapeutics by targeting microtubules. Microtubules are the key structural and functional elements of neurons and have been found to be closely associated with neurodegenerative disorders like AD due to their association with tau. Tau is a microtubule associated protein whose abnormal phosphorylation leads to microtubule destabilization giving rise to variable tauopathies associated with different neurodegenerative disorders. Due to this association of microtubules with tau and their importance in neurons, microtubules can be considered as one of the important supplementary targets for designing future neurotherapeutics.

KEYWORDS: *Microtubules, neurotherapeutics, tauopathies, amyloid beta, neuron*

Microtubule stabilization has never really been considered as an avenue for development of neurotherapeutics in Alzheimer's disease (AD). Most of the focus regarding the development of drugs has been on the amyloid hypothesis with not much clinical success. A number problems have been identified regarding the failure of the Aβ targeting drugs; nonetheless, still more thorough research and probing in that direction is needed to formulate better drug candidates.[1] Therefore, a more realistic target like microtubules could serve our purpose. Microtubules (MTs) are polymers of hetero-dimeric α and β tubulins that maintain the embroidered morphology of the neurons and undergo continuous phases of growth and shrinkage to attain dynamicity in its structure. This dynamic instability is mostly regulated by plus end tracking proteins (+TIPs), which gather at the growing ends of MTs and control growth and development of neurons. Apart from their roles in the different stages of neuronal development like neurite initiation, migration, polarization, and differentiation, they additionally have a wide repertoire of functions.[2] Here, we highlight some of these functions and why microtubules can be considered as key players of the neurons:

(1) Neurons have complex branched morphology consisting of axons and dendritic arbors, which are further interconnected with other neurons through synapses. In order to maintain this exaggerated network, a robust transport mechanism is required. Microtubules with the help of motors proteins (kinesin and dynein) fulfill that function by serving as railway tracks for the intracellular transport of several neuronal cargos like organelles, neurotransmitter receptors, various cell signaling molecules, synaptic vesicle precursors, and mRNAs. MT organization also confers specificity in their transport of cargo into axons and dendrites.[2] The perfect examples of these are the minus-end- directed motor dynein and plus-end directed motor kinesin-1, which selectively transports to the dendrites and axons, respectively.

(2) In order to develop the much needed functional interconnections, the neurons need to reach out to each other, making neurite outgrowth an extremely important feature. Apart from several other extracellular cues, the most crucial step in the formation of these neurite processes for better interconnectivity is taken care of by the pushing and pulling forces of the MTs and actin filaments present in the extending neurites which ultimately leads to membrane protrusions.[2]

(3) Other than neurite outgrowth and intracellular cargo transport in neurons, MT stabilization is critical for axonal differentiation, outgrowth, and regeneration in the case of any injury. The MT establishes interactions with actin, other adhesion complexes, and many plus-end tracking proteins (+TIPs) in order to drive the advancement of growth cone and axonal elongation.

(4) Lastly, MT stabilization may also contribute toward formation of synapse as reported in some studies like the one by Roos et al., whereby they have shown how a motile growth cone in the neuromuscular junction in Drosophila can be converted into a motile growth cone through MT loop formation in the growth cone.[3]

It has been commonly observed that, in most of the neurodegenerative diseases, there is a progressive loss of microtubule mass from axons and dendrites. Considering the above-mentioned roles of microtubules in neurons, microtubule stabilization is likely to become the new horizon for the development of future neurotherapeutics (Figure 1). One of the more prevalently known methods toward this venture

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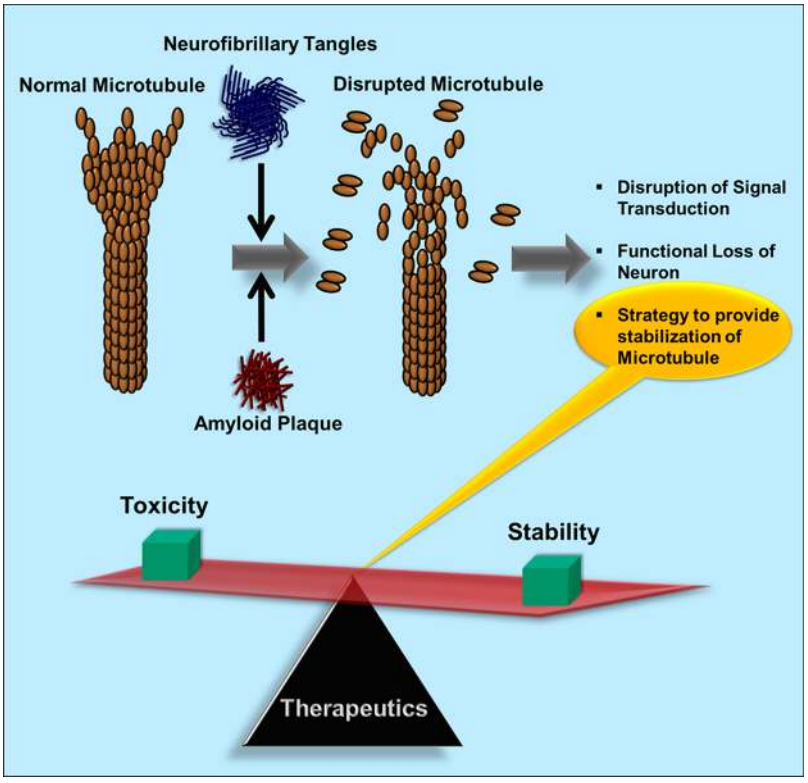

Figure 1. Schematic illustration highlights that both neurofibrillary tangles and amyloid plaque are associated with microtubule disruption, which resulted in the loss of neuron function. Thus, design and development of neurotherapeutics is essential, which can carefully balance between the toxicity and stable microtubule dynamics.

would be the development of tau protein targeted therapeutics. Tau as we know is a microtubule associated protein found in abundance in the neurons of the central nervous system (CNS) and is thought to play a critical role in the stabilization of MTs. Tau protein plays a key role in regulation of microtubule dynamics, intracellular axonal transport, and neurite outgrowth. All these functions of tau are controlled through phosphorylation, in which any abnormal phosphorylation leads to microtubule dysfunction causing neurodegenerative disorders referred to as tauopathies.[4] In the case of neurodegenerative diseases like AD, tau gets abnormally acetylated and hyperphosphorylated, detaches from the microtubule lattice causing catastrophic activation and collapse of the entire microtubule fabric. This above microtubule disintegration occurs through a loss-of-function mechanism whereby the stable domains of the microtubules are destabilized, rendering the microtubule mass labile. As this loss of microtubule mass would take years, another model of tauopathy has been put forward which states that as tau dissociates, microtubule severing proteins like katanin get activated which then sensitizes microtubules. In another separate gain of function mechanism, the tauopathies are characterized by the intracellular accumulation of hyperphosphorylated tau fibrils wherein the tau deposits as insoluble aggregates are believed to result in a loss of tau function that leads to MT destabilization. This could be due to the hyperactivation of kinases regulating microtubule-regulatory proteins or sequestration of microtubule stabilizing proteins by the abnormal tau filaments. Due to the intense association of microtubule stability with tauopathies, it has sparked interest in the development of microtubule stabilizing drugs. Already known some of the microtubule stabilizing drugs has shown promising effects like epithilone D which causes microtubule stabilization like the taxols but unlike taxols it can also cross the blood brain barrier.[4] While epithilone D is just one of the already known microtubule stabilizing drugs that have been tested, a library of novel molecules including microtubule stabilizing peptides and peptoids are being synthesized and tested. In this direction, we adopted an innovative strategy by designing an octapeptide, "NEVFLDTQ" (PS3) from the taxol binding pocket of β-tubulin.[5] PS3 showed strong binding with tubulin in the in vitro assays with a binding constant of 3.8×10^5 M^{-1}. When applied to PC12 derived neurons, it showed microtubule polymerization, increased expression of acetylated tubulin, neurite outgrowth and neuroprotection against anti-NGF mediated toxicity.[5] What is of consequence here is that in spite of being carved out of the taxol pocket, it does not cause toxicity unlike other taxol drugs which may be attributed to its moderate microtubule binding affinity which is 225 times lower at 4 °C and 47500 times lower at 37 °C as compared to taxol.[5] Hence while designing drugs targeted for microtubule stabilization, it must be remembered that while trying upholding the stability of the microtubule mass so as to prevent any loss of microtubule mass, we must always remember to never comprise on its dynamicity. If our drug blocks this microtubule dynamics, then it will turn out like a poison like taxol for the cell.

In summary, microtubules are very important structural and functional units of neurons. They are the basic pillars which hold the spectacular elaborate structures of neurons and help in the formation of neuronal networks by aiding neurite initiation and outgrowth. Any form of fiddling with this microtubule lattice whether in the form of hyperphosphorylation of tau or any other stress leads to devastating

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consequences for the neurons as observed in neurodegenerative diseases like AD. In these dark times when drugs targeting amyloid hypothesis have failed to produce any significant clinical output, preservation of this microtubule lattice could be a new beacon of light in the development of neurotherapeutics and could well serve as a new supplementary target.

AUTHOR INFORMATION

Corresponding Author

*Fax: +91-33-2473-5197/0284. Tel: +91-33-2499-5872. E-mail: sghosh@iicb.res.in.

ORCID

Gaurav Das: 0000-0002-8432-5384

Surajit Ghosh: 0000-0002-8203-8613

Notes

The authors declare no competing financial interest.

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