Commentary

Dendritic TAU-telidge

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A R T I C L E   I N F O

In this issue of *EBioMedicine*, Kobayashi et al. demonstrate the presence of tau mRNA in the dendritic bouton, and induction of dendritic tau translation and phosphorylation following stimulation of the ionotropic (NMDA & AMPA) glutamate receptors (Kobayashi et al. 2017). This work, emanating from the laboratory of Akihiko Takashima, adds an important chapter to the accumulating evidence demonstrating an active role for tau in the biology of the dendritic bouton and synaptic signaling.

Under normal conditions, the vast majority of tau exists in the axon. This means that bulk analysis of tau protein will largely reflect the properties of axonal tau. However, it is now clear that tau also functions in neuronal domains other than the axon. Ittner and colleagues demonstrated that tau protein exists in the dendrite and moves into the dendritic bouton with glutamatergic stimulation (Ittner et al. 2016). Dendritic tau is responsive to phosphorylation by Fyn and by PKCγ (Ittner et al. 2016). The current work from Takashima's group brings GSK3β into the picture as an additional regulator of dendritic tau, phosphorylating S202, which is adjacent to the site phosphorylated by PKCγ, at S205. In each case, phosphorylation of tau is stimulated by activation of the NMDA receptor, signaling via calcium. Takashima's group extends the story further by using the protein synthesis inhibitor cycloheximide to demonstrate that NMDAR and AMPAR activation also leads to stimulation of tau translation in the dendritic bouton. The coupling of initiation of tau translation with stimulation of tau phosphorylation provides an important independent means of confirmation of the role of tau in post-synaptic activity. Thus, the evidence demonstrating a role for tau in dendritic synaptic activity now includes evidence at both protein and mRNA levels.

The somatodendritic localization of tau has been apparent since tau was first shown to be the major component of neurofibrillary tangles, a pathological hallmark of Alzheimer's disease, in the 1980′s. The reason for localization of tau away from the axon was rarely questioned previously, and just assumed to result from the inability of a degenerating neuron to properly distribute its proteins. In 2010, tau was show to be normally synthesized in the somatodendritic compartment, where it actively accumulates during stress, instead of shuttling to the axon (Hoover et al. 2010; Li et al. 2011). The presence of tau mRNA in the soma provides a strong basis for the presence of tau in the dendritic arbor; one only need to invoke trafficking by RNA transport granules containing RNA binding proteins (RBPs). The current report by Kobayashi et al. demonstrate colocalization of tau mRNA with two RBPs, stau1 and FMRP, that function as transport proteins.

The role of RBPs in tau biology turns out to be profoundly important. All RNA is trafficked throughout the neuron in neuronal trafficking granules that are composed of RNA binding proteins and mRNA. These RBPs then appear to exhibit a natural tendency to coalescence into a state resembling lipid droplets or vesicles, except there is no lipid present(Alberti and Hyman 2016). Rather, the proteins themselves contain low complexity domains that tend to reversibly "aggregate", which allows the RBP/RNA complexes to form granules, which can be considered to be membraneless organelles. These membraneless organelles appear to form through a process termed liquid-liquid phase separation, and enable the organization of many structures in the cell, such as the nucleolus, P bodies, transport granules, nuclear speckles and possible even transcription complexes. Stress granules constitute another class of RNA granule. These granules are also RBP/RNA complexes that sequester non-essential mRNA during stressful conditions, allowing the cell to direct protein synthesis towards cytoprotective proteins. (Ash et al. 2014; Panas et al. 2016). It's easy to imagine that stress granules are important for disease, which are characterized by persistent stress; mutations in RBPs that increase the tendency of these proteins to aggregate cause ALS and myopathies, possibly because of persistent stress granules that become pathological.

Tau was recently shown to participate in stress granule biology, and persistence of stress granules stimulates tau aggregation (Vanderweyde et al. 2016). RNA binding proteins are present in neurofibrillary pathology in mouse models of tauopathy and in human cases of tauopathy, including Alzheimer's disease (Vanderweyde et al. 2016). Persistent stress granules directly stimulate tau aggregation and tau stimulates stress granules, indicating that the biology is bi-directional. Indeed, stimulation of stress granule formation appears to be an important biological function of tau. These accumulating data combined with the recent work by Kobayashi et al., the "mislocalization" of tau to the

somatodendritic arbor appears to occur by biological design rather than as a pathological mistake.

The cumulative impact of all of these studies broadens our perception of the roles of tau in biology and disease. It is now apparent that tau exists in many different domains within the neuron, and the function of tau varies depending on the neuronal domain being considered. The expanding biology of tau is apparent in recent studies demonstrating that tau knockout impairs synaptic plasticity and interferes with neuronal and behavioral response to stress (Lopes et al. 2016). A reduced stress response dampens the toxicity of Aβ but might also leave the neuron less able to cope with other types of stress (Vossel et al. 2010). Managing the excessive tau-directed stress response in AD and other tauopathies might end up being analogous to treatment of hypertension where the therapeutic goal is to reduce persistently high blood pressure, but not eliminate blood pressure. In the same way, the goal for treating neurodegenerative disease might be to reduce a persistently hyperactive translational stress response without eliminating the stress response.

Conflicts of Interest Statement

Benjamin Wolozin is Co-Founder and Chief Scientific Officer of Aquinnah Pharmaceuticals Inc.

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