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Tau Propagation, Different Tau Phenotypes, and Prion-like Properties of Tau

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Sanders et al. (2014) demonstrate in this issue of *Neuron* that the natively unfolded protein tau can propagate indefinitely in distinct stable strains, therefore supporting the general idea that tau has prion-like properties, with implications for Alzheimer's disease and other tauopathies.

Tau is a microtubule-associated protein that is generally considered to be "unfolded" in its native state (Schwalbe et al., 2014), although it clearly adopts specific conformations when associated with microtubules, or when it is "misfolded" in the setting of forming inclusions in neuronal soma as neurofibrillary tangles in Alzheimer's disease or as different inclusions in other tauopathies. Morphologically, these various tauopathies are distinct, allowing neuropathologists to readily distinguish the tangles of Alzheimer's disease from Pick bodies in frontotemporal dementia or argyrophillic grains in argyrophillic grain disease (Feany and Dickson, 1996). How these different morphologies arise from the same protein has been uncertain, although in any individual patient one type of morphology tends to predominate. In addition to the differences in morphology, the various types of inclusions are also differentiated by the specific neuronal populations and even brain areas affected and often by the isoform (e.g., 4 repeat versus 3 repeat tau) and phosphorylation state of tau. Both genetic (mutation and splice form changes) and sporadic forms of tauopathies occur, each with a characteristic neuroanatomical pattern of "spread" (Arnold et al., 2013). Some of the disorders classically are strikingly asymmetric, strongly affecting either the right or left hemisphere, another puzzling characteristic especially in instances where the cause is genetic.

The current exciting study by Sanders et al. (2014), building on elegant work by Clavaguera and colleagues (Clavaguera et al., 2013), addresses some of these issues. The data suggest that one way these morphological and clinical variants occur is through propagation of individual "strains" of misfolded tau. They demonstrate that tau can adopt different conformational states and that those conformational states are stable and can be propagated by recruitment of native tau to indefinitely cause new inclusions to form in inoculated cells in culture, or predisposed neurons in brain, over multiple rounds of seeding and spreading. Distinct strains can be obtained by clonal selection in vitro or by utilizing tau derived from human tauopathy cases of various diseases, in each case showing stable conformational integrity analogous to prion "strains." This supports the notion that tau has prion-like properties, since the formation of conformationally stable strains is a property of other prion-like molecules. Moreover, the data demonstrate that different conformations can occur in different pathological settings and therefore imply that these conformations might account for the different clinical and neuropathological characteristics of the various tauopathies.

Another example of templated misfolding of tau seems to occur in the observed transsynaptic spread of the presumed pathogenic species in mouse models (de Calignon et al., 2012; Liu et al., 2012); this has been suggested as the underlying mechanism of the march of tau neurofibrillary tangles from limbic areas to broader neocortical targets in a hierarchical pattern across anatomically distinct pathways in Alzheimer's disease. Importantly, in humans the data suggest that the transsynaptic spread phenomenon is a combination of the presence of specific, unique characteristic tau conformers and a recipient neuron that can act as the host. For example, while many of the hippocampal neurons that develop neurofibrillary tangles in Alzheimer's disease are strongly interconnected, dentate gyrus granule cells, which receive the bulk of the perforant pathway projection from the early affected entorhinal cortex, are relatively resistant (Hyman et al., 1984). On the other hand, tau inclusions called Pick bodies are classically present in frontotemporal dementia, despite the fact that it is exactly these same granule cells in the dentate gyrus that are resistant to the alternatively folded form of tau found in neurofibrillary tangles. The observation of distinct strains in tauopathies that have differential cellular and brain region predispositions suggest unique relationships between specific misfolded tau species and host cell characteristics that are largely unexplored.

Many questions remain to be answered, both in tauopathies and in the broader context of prion disorders and other neurodegenerative diseases. How are different "strains" initiated in individual patients with different diseases? Why would different brain areas and neuronal subtypes be selectively vulnerable for different forms of inclusions? What types of insults might cause the initial misfolding events that are then propagated across neural systems? Why would this process lead to a dramatically asymmetric pattern of neurodegeneration in some diseases, while others are quite symmetric? Why would specific, and distinct, neural systems be involved based on the exact tau "strain" or conformation of the molecule? How does the misfolded molecule escape cellular surveillance mechanisms? Are the misfolded tau molecules toxic, and are various strains differentially toxic to

different subclasses of neurons? How do transcriptional (splicing) and posttranslational alterations of tau fit into this newly evolving view of tau's conformational complexity? And does tau toxicity occur as a consequence of its accumulation in the cell body as an aggregate, or perhaps more directly as a synaptotoxic species that is distinct from the aggregating forms (Irwin et al., 2013; Tai et al., 2012)?

The current data clearly demonstrate that tau can form strains that retain their biological characteristics over successive inoculations and also that these strains can induce inclusions in neurons, so that misfolded tau appears to be transmissible both across the synapse within a brain and also between brains. Tau therefore shares important characteristics of prions. However, there are critical aspects of the data that imply differences between tau biology and classical prion diseases and suggest caution in interpreting tau as an example of a prion, and, by extension, tauopathies and Alzheimer's disease to be prion diseases in the way that these terms are commonly used—as communicable diseases. Importantly, as noted by Sanders et al. (2014), infectivity in humans has not been shown. The species barrier present in so many examples in prion disease appear not to be the case for tau, which can recruit endogenous mouse tau to mutant human protein (de Calignon et al., 2012). Strictly speaking, it is not yet clear that fibrillar tau is neurotoxic, and instead either soluble tau species, or mislocalized tau, have been suggested to lead to neural impairments (Frost et al., 2014; Kopeikina et al., 2012; Kuchibhotla et al., 2014; Kumar et al., 2014). Therefore, at this point it appears that mechanisms of tau fibril spread appear to share biological systems analogous in many ways to prion spreading, but it remains to be shown whether tau has all prion-like properties—including human to human infectivity, and toxicity, and thus whether it should be considered a member of the prion family of protein misfolding disorders or a true prion disease. Nonetheless, the current data strongly support the idea that tau—and especially extracellular tau—is a viable target for therapeutic interventions (Yanamandra et al., 2013).

REFERENCES

Arnold, S.E., Toledo, J.B., Appleby, D.H., Xie, S.X., Wang, L.S., Baek, Y., Wolk, D.A., Lee, E.B., Miller, B.L., Lee, V.M., and Trojanowski, J.Q. (2013). J. Comp. Neurol. *521*, 4339–4355.

Clavaguera, F., Akatsu, H., Fraser, G., Crowther, R.A., Frank, S., Hench, J., Probst, A., Winkler, D.T., Reichwald, J., Staufenbiel, M., et al. (2013). Proc. Natl. Acad. Sci. USA *110*, 9535–9540.

de Calignon, A., Polydoro, M., Suárez-Calvet, M., William, C., Adamowicz, D.H., Kopeikina, K.J., Pitstick, R., Sahara, N., Ashe, K.H., Carlson, G.A., et al. (2012). Neuron *73*, 685–697.

Feany, M.B., and Dickson, D.W. (1996). Ann. Neurol. *40*, 139–148.

Frost, B., Hemberg, M., Lewis, J., and Feany, M.B. (2014). Nat. Neurosci. *17*, 357–366.

Hyman, B.T., Van Hoesen, G.W., Damasio, A.R., and Barnes, C.L. (1984). Science *225*, 1168–1170.

Irwin, D.J., Cohen, T.J., Grossman, M., Arnold, S.E., McCarty-Wood, E., Van Deerlin, V.M., Lee, V.M., and Trojanowski, J.Q. (2013). Am. J. Pathol. *183*, 344–351.

Kopeikina, K.J., Hyman, B.T., and Spires-Jones, T.L. (2012). Transl. Neurosci. *3*, 223–233.

Kuchibhotla, K.V., Wegmann, S., Kopeikina, K.J., Hawkes, J., Rudinskiy, N., Andermann, M.L., Spires-Jones, T.L., Bacskai, B.J., and Hyman, B.T. (2014). Proc. Natl. Acad. Sci. USA *111*, 510–514.

Kumar, S., Tepper, K., Kaniyappan, S., Biernat, J., Wegmann, S., Mandelkow, E.M., Müller, D., and Mandelkow, E. (2014). J. Biol. Chem. Published online May 13, 2014. http://dx.doi.org/10.1074/jbc.M114.554725.

Liu, L., Drouet, V., Wu, J.W., Witter, M.P., Small, S.A., Clelland, C., and Duff, K. (2012). PLoS ONE *7*, e31302.

Sanders, D.W., Kaufman, S.K., DeVos, S.L., Sharma, A.M., Mirbaha, H., Li, A., Barker, S.J., Foley, A.C., Thorpe, J.R., Serpell, L.C., et al. (2014). Neuron *82*, this issue, 1271–1288.

Schwalbe, M., Ozenne, V., Bibow, S., Jaremko, M., Jaremko, L., Gajda, M., Jensen, M.R., Biernat, J., Becker, S., Mandelkow, E., et al. (2014). Structure *22*, 238–249.

Tai, H.C., Serrano-Pozo, A., Hashimoto, T., Frosch, M.P., Spires-Jones, T.L., and Hyman, B.T. (2012). Am. J. Pathol. *181*, 1426–1435.

Yanamandra, K., Kfoury, N., Jiang, H., Mahan, T.E., Ma, S., Maloney, S.E., Wozniak, D.F., Diamond, M.I., and Holtzman, D.M. (2013). Neuron *80*, 402–414.