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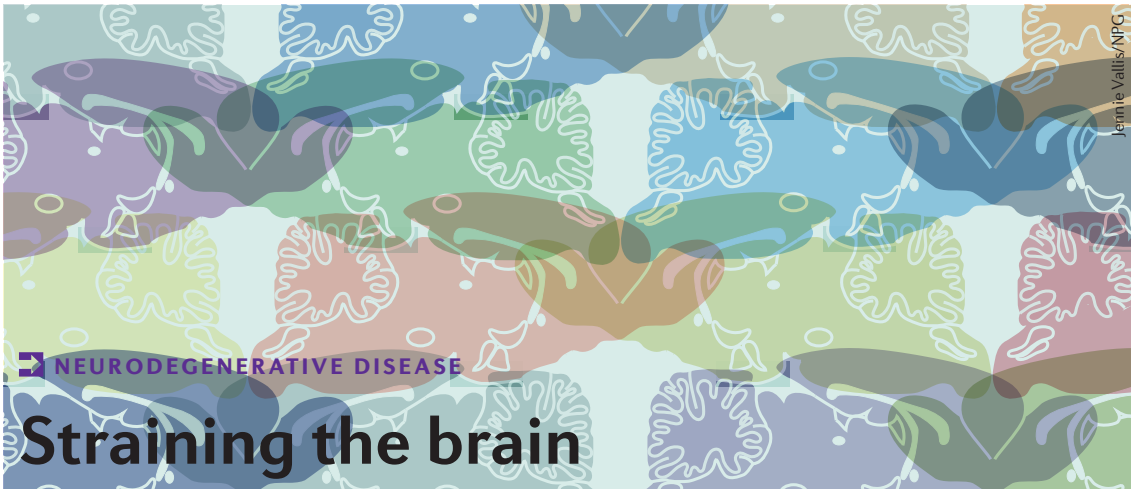

NEURODEGENERATIVE DISEASE

Straining the brain

The deposition of tau protein in the brain is a feature of several neurodegenerative diseases. These so-called tauopathies show differences in tau inclusion phenotypes, and in the distribution and speed of pathology development, but what confers this variation is unclear. Based on various findings, tau aggregates have been hypothesized to be transferred between cells via neural connections and trigger monomeric tau in the receiving cell to aggregate (so-called seeding), thereby propagating tau pathology. Now, Diamond and colleagues show that inoculation of mice expressing a mutant form of tau (PS19 mice) with different strains of aggregated tau induces different types of tau neuropathologies that form at differing rates and with varying distributions, indicating that the strains themselves can confer distinct pathologies and providing further evidence for this hypothesis.

The authors previously generated a stable cell line that expressed a disease-associated fragment of tau and showed that it could be used to propagate strains of aggregated tau that were extracted from different sources. Here, they treated such cells with tau aggregates from humans, mice or recombinant tau preparations to form cell lines that propagated the given aggregates. Through screening, they identified 18 putative strains of aggregated tau that differed in terms of inclusion morphology, proteolytic fragmentation patterns and/or seeding ability.

Morphologically, some of the strains were associated with single tau inclusions close to the nucleus, whereas others were associated with nuclear inclusions or cytoplasmic fibrils, among other structures. Proteolytic cleavage experiments revealed that different strains had different structural 'fingerprints' and that the inclusion morphology was insufficient to predict the cleavage pattern of a strain. Seeding assays showed that different strains varied in their ability to induce the aggregation of monomeric mutant tau in cell lines and cultured hippocampal neurons, and that inclusion morphology could also not predict seeding activity.

> “Seeding assays showed that different strains varied in their ability to induce the aggregation of monomeric mutant tau in cell lines and cultured hippocampal neurons”

The authors next generated a cell line expressing fragments of mutant tau linked to fluorescence resonance energy transfer (FRET) biosensors, exposed these cells to the various strains of tau and examined the growth of cells containing tau aggregates (as determined by FRET). This approach revealed that seeding activity correlated with the inhibition of cellular growth. Interestingly, seeding activity did not correlate with the total or insoluble level of tau, suggesting that, in dividing cells, the strcuture of a strain is an important determinant of its seeding activity and toxic effects.

Could the variation in the properties of the strains *in vitro* account for the neuropathological variation that is observed in tauopathies *in vivo*? To address this question, the authors injected tau strains into the hippocampus of PS19 mice. The different strains were associated with different types of intracellular hippocampal pathology, with those showing the highest seeding activity often being associated with the most striking inclusions and widespread pathological distribution.

Subsequently, the authors inoculated various mouse brain regions with a selection of these strains to explore whether the strains affect specific brain regions. After 5 weeks, some strains with high seeding activity caused pathology at all the injection sites, whereas a strain with weaker activity just showed pathology in the hippocampus. However, some strains did not adhere to this apparent seeding activity–pathology relationship, indicating that factors other than seeding activity also determine the vulnerability of specific brain regions to certain tau strains.

Finally, the authors examined how quickly tau pathology spreads after the injection of strains into the hippocampus of young PS19 mice. Although all strains eventually induced pathology in the contralateral hippocampus, those associated with the highest seeding activity spread to this region much more quickly than the other strains and showed rapid spreading to other regions at the earliest time point assessed.

Together, these findings suggest that different strains of tau may account for at least some of the differences between tauopathies in terms of the brain regions affected by tau pathology and the rate of its development.

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ORIGINAL ARTICLE Kaufman, S. K. *et al.* Tau prion strains dictate patterns of cell pathology, progression rate, and regional vulnerability *in vivo*. *Neuron*, http://dx.doi.org/10.1016/j.neuron.2016.09.055 (2016)