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NEURODEGENERATIVE DISEASE

New *in vivo* evidence that different tau strains cause different diseases

> these results could have enormous implications for future clinical research

Distinct strains of tau cause different pathologies in mice, according to a new study published in *Neuron*. The work provides strong evidence that different strains of tau can explain the origin of different tauopathies. The findings not only provide the basis for new insights into the pathogenesis of these diseases, but also have important implications for the design of anti-tau therapeutics.

Marc Diamond, who led the new study, and his colleagues were among the first to suggest that tau aggregates could function as prions, acting as seeds for further propagation of pathology throughout the brain. In the past few years, they have gone on to provide evidence to support this hypothesis.

"We have demonstrated that, for all intents and purposes, tau behaves as a bona fide prion," explains Diamond. "It can propagate distinct structures indefinitely in cells and animals, these structures — or 'strains' — can be stably transmitted via serial inoculation, and they produce distinct pathological patterns in mice."

In their new work, Diamond and co-workers aimed to gain further insight into the pathological consequences of different tau strains. They started by generating a library of strains in a previously established cell-based system. Cells were treated with recombinant tau aggregates or aggregates from mouse or human brain samples, and strains were identified on the basis of distinct inclusion morphologies. In total, the researchers isolated 18 strains of tau, which they analysed *in vitro* to confirm that the tau strains were distinct from one another.

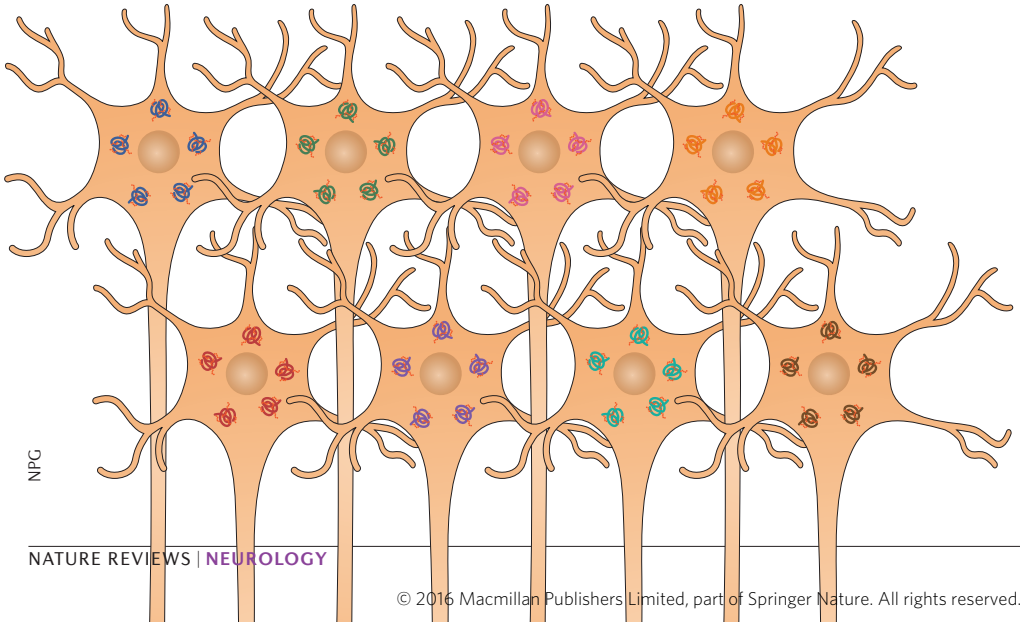
Each tau strain was then injected into the hippocampus of PS19 mice, which express human tau with a single disease-associated mutation. Brain pathology was analysed 4, 8 and 12 weeks later. Each strain produced a unique pathology, characterized by different rates of propagation through the nervous system, and distinct patterns of neuronal pathology. Furthermore, injection of the tau strains into different brain regions showed that some induced pathology at every site, whereas others induced pathology only at some sites.

"Each strain produced a unique disease in mice," summarizes Diamond. "This answers fundamental questions in the field: how can we get different diseases due to tau, why are some neurons vulnerable to disease and others are not, and why do some diseases progress faster than others?"

The findings suggest that different tau strains are likely to underlie different tauopathies in humans, but Diamond says that making use of this knowledge presents several challenges. In particular, the dominant strains that are present in individual patients will need to be identified, ideally before symptoms develop. He also says that more work is needed to understand how the structural properties of tau strains lead to the variety of pathological consequences.

"Nevertheless, these results could have enormous implications for future clinical research," Diamond continues. "Many pharmaceutical companies are developing anti-tau antibodies to treat tauopathy. Our work says that there is an enormous diversity of tau prion conformations, and that this needs to be taken into account when designing therapeutic antibodies or other small molecules that target tau prion activity, and when determining which patients are going to be treated with them."

Ian Fyfe



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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)

FURTHER READING Iqbal, K. *et al.* Tau and neurodegenerative disease: the story so far. *Nat. Rev. Neurol.* **12**, 15–27 (2016)