Computational modeling of tau pathology spread reveals patterns of regional vulnerability and the impact of a genetic risk factor.

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Description

Neuropathological staging studies have suggested that tau pathology spreads through the brain in Alzheimer's disease (AD) and other tauopathies, but it is unclear how neuroanatomical connections, spatial proximity, and regional vulnerability contribute. In this study, we seed tau pathology in the brains of nontransgenic mice with AD tau and quantify pathology development over 9 months in 134 brain regions. Network modeling of pathology progression shows that diffusion through the connectome is the best predictor of tau pathology patterns. Further, deviations from pure neuroanatomical spread are used to estimate regional vulnerability to tau pathology and identify related gene expression patterns. Last, we show that pathology spread is altered in mice harboring a mutation in leucine-rich repeat kinase 2. While tau pathology spread is still constrained by anatomical connectivity in these mice, it spreads preferentially in a retrograde direction. This study provides a framework for understanding neuropathological progression in tauopathies.

Neurodegenerative Diseases

Neurodegenerative diseases, including Alzheimer's Disease (AD) and Parkinson's Disease (PD), are estimated to affect over 60 million people worldwide. Neurological symptoms and the presence of pathological protein inclusions are used to categorize the two diseases. However, there exists substantial overlap in both symptoms and pathologies, especially as these diseases progress. Tau pathology, while diagnostic of AD and other primary tauopathies, appears prominently in PD, PD Dementia (PDD), and dementia with lewy bodies, where it correlates with α-synuclein pathological burden and cognitive decline. These data suggest that multiple pathologies may act additively to influence disease progression and that underlying risk factors for one pathology may confer risk for additional pathologies [1].

Postmortem neuropathology studies have demonstrated that patients with more severe clinical AD and PDD have elevated levels of pathological tau in an increasing number of regions of the brain. The stages of observed tau pathology (beginning in the locus coeruleus, then transentorhinal and entorhinal cortex, and moving through the hippocampus and cortical regions) are suggestive of pathology "spreading". Pathological tau from human brains injected into Nontransgenic (NTG) mice can be internalized into nearby neurons, initiating misfolding and hyperphosphorylation of endogenous mouse tau in a prion-like manner into intraneuronal inclusions resembling those from human disease tissue. Over time, tau pathology can be found in more regions of the mouse brain connected to the injection site suggesting that tau is spreading. How tau pathology spreads has been a matter of debate because it has not been possible to disambiguate the contribution of neuroanatomical connectivity, spatial proximity of regions, and intrinsic neuronal vulnerability. Recent studies based on mathematical modeling of human brain suggest that anatomical connectivity serves as a strong predictor of brain atrophy or general pathology patterns in neurodegenerative diseases [2].

LRRK2 Mutation Risk Analysis

In the current study, we investigated processes underlying the development and spread of tau pathology. We developed a methodology for reproducibly quantifying tau pathology in 134 regions of the mouse brain following an intracranial injection of pathogenic tau. Tau pathology in this model begins slowly, first affecting the injection site and highly connected regions. As time progresses, more regions are affected. Once affected, regions show a nearly linear increase in tau pathology over time. While this atlas of pathology is informative, it is still not possible to discern mechanisms of pathology spread without considering the brain as a network of interconnected regions. We therefore used computational analysis of spatiotemporal tau pathology patterns. We found that tau pathology spread is best explained by diffusion along neuroanatomical connections in a bidirectional manner [3]. Residual variance in the data that was not well explained by connectivity was used to generate estimates of differential vulnerability to tau in measured regions. Comparison of regional vulnerability to regional gene expression identified several previously unidentified candidate genes that may control susceptibility to tau pathology [4]. To further assess the utility of quantitative pathology and network modeling, we analyzed a mouse expressing the LRRK2 mutation. This mutation is a risk factor for PD, but many of these patients exhibit tau pathology. LRRK2 mice exhibit a bias toward retrograde spread of tau pathology, providing insight into the network-level impact of cell biology events. This work provides a framework for understanding the spread of pathological tau throughout the brain and investigating the impact of genetic risk factors on pathology progression [5].

References

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