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Non-cell-autonomous neurodegeneration and tau spreading in two models of tauopathy

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Tauopathies, such as Alzheimer's disease and frontotemporal dementia (FTD), are characterised by hyperphosphorylation, misfolding and aggregation of the microtubule-associated protein tau. In the disease process, tau pathology typically first appears in specific, confined brain regions but eventually involves most areas, leading to broad functional impairment and neuronal loss. The spatiotemporal pattern in which tau lesions propagate through the brain is constant and follows major neuronal pathways, suggesting non-cell-autonomous processes such as the transfer of protein between connected neurons. Such mechanisms might provide targets for new treatment strategies but are poorly understood. Moreover, available in vivo and in vitro models for studying this aspect of tauopathies are limited.

Here, I spatially related patterns of tau pathology with neuronal loss using K369I mutant tau transgenic K3 mice. Animals show early histopathology and present with motor deficits including parkinsonism and cerebellar ataxia, the latter of which has not been studied before. Immunohistochemical examination of K3 cerebellar circuits revealed overlapping areas of transgene expression, tau hyperphosphorylation and neurodegeneration in the cortical granule layer, subcortical fibres as well as in deep cerebellar and pontine nuclei. Notably, K3 mice displayed a pronounced, age-dependent loss of cerebellar baskets without expression of mutant tau in according basket cells, indicating non-cell-autonomous pathomechanisms; these likely involve adjacent afferent fibres, which contain high levels of phosphorylated transgene.

In the second part of this study, I used compartmented cultures of murine hippocampal neurons within microfluidic devices to examine the inter-cellular spreading of tau in vitro. By applying a modified lentiviral vector, genes for native and K369I mutant human tau were selectively introduced in one compartment of cultures, thereby creating ordered neuronal networks between transgenic and native cells. Immunocytochemical studies of these networks showed that both native and K369I mutant tau transferred to native neurons via synaptic connections.

The present study shows the existence and relevance of non-cell-autonomous mechanisms in the pathogenesis of tauopathies in vivo and in vitro. The finding of inter-neuronal transfer of the traditionally intra-cellular protein tau, together with previous descriptions of its susceptibility to templated conformational change, may have important implications for the understanding of how disease spreads throughout the brain. Further studies are needed to identify the transferred tau species and the responsible cellular machinery, which might eventually be modified pharmacologically. Both models that were established here may be particularly useful for this purpose.