Genome-wide CRISPRi screening reveals regulators of Alzheimer's tau pathology shared between exosomal and vesicle-free tau seeds

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The aggregation of the microtubule-associated protein tau is a defining feature of Alzheimer's disease (AD) and other tauopathies. Tau pathology is believed to be driven by free tau aggregates and tau carried within exosomes, which both propagate trans-synaptically and induce tau pathology in recipient neurons by a corrupting process of seeding. Control of tau propagation by targeting either exosomes or vesicle-free tau has been proposed as a viable therapeutic strategy. It is therefore crucial to identify regulators of tau pathology that control both forms of tau seeding, covering shared entry routes and potentially conferring more complete protection against seeded tauopathy.

Here, we performed a genome-wide CRISPRi screening in tau biosensor cells to discover novel regulators of seeded tau aggregation induced by exosomal and vesicle-free tau seeds. We identified ANKLE2, BANF1, NUSAP1, EIF1AD, and VPS18 as top validated regulators that restrict tau aggregation initiated by both forms of tau seeding. Interestingly, both ANKLE2 and BANF1 more robustly affected tau seeding caused by exosomal tau than by free aggregates. Furthermore, none of our validated hits affected the uptake of either form of tau seeds, supporting the notion that they operate through a cell-autonomous mechanism downstream of the seed uptake. Lastly, validation studies with human brain tissue revealed that several of the identified protein hits are downregulated in the brains of AD patients, suggesting that their decreased activity may be required for the emergence or progression of tau pathology in the human brain.

In conclusion, we have validated novel negative regulators that oppose the formation of tau aggregates. Some of these genes are downregulated in AD patients, which may imply a functional role in the emergence of tau pathology in humans. Future experiments will reveal how these genes regulate tau aggregation, and why tau seeds in exosomes are more affected by specific genes.