Novel repertoire of tau biosensors based on NanoBiT technology to monitor pathological tau transformation and seeding activity in living cells.

Cecon E.
Institut Cochin, Inserm U1016, CNRS UMR 8104, Université de Paris, Paris, France

Aggregates of the tau protein are a well-known hallmark of several neurodegenerative diseases, collectively referred to as tauopathies, including frontal temporal dementia and Alzheimer's disease (AD). Monitoring the transformation process of tau from physiological monomers into pathological oligomers or aggregates in a high-throughput, quantitative manner and in a cellular context is still a major challenge in the field. Identifying molecules able to interfere with those processes is of high therapeutic interest.
We have developed a series of inter- and intramolecular tau biosensors based on the highly sensitive Nanoluciferase (Nluc) binary technology (NanoBiT, Promega) able to monitor the pathological conformational change and self-interaction of tau in living cells (Cecon et al., Elife. 2023, 12:e78360, PMID: 36917493). Our repertoire of tau biosensors reliably reports i. molecular proximity of physiological full-length tau at microtubules; ii. changes in tau conformation and self-interaction associated with tau phosphorylation, as well as iii. tau interaction induced by seeds of recombinant tau or from mouse brain lysates of a mouse model of tau pathology. By comparing biosensors comprising different tau forms (*i.e.* full-length or short fragments, wild-type, or the disease-associated tau(P301L) variant) further insights into the tau transformation process are obtained. Proof-of-concept data for the high-throughput suitability of these innovative NanoBiT tau biosensors for the identification of molecules interfering with the pathological tau transformation processes could also be obtained. This novel repertoire of tau biosensors is aimed to boost the disclosure of molecular mechanisms underlying pathological tau transformation in living cells and to discover new drug candidates for tau-related neurodegenerative diseases.