LSU Health Sciences Center NEW ORLEANS

School of Medicine

Neuroscience Center of Excellence

Chancellor's Award Lecturer *in Neuroscience*

Co-Sponsored by the Local Chapter of the Society for Neuroscience (GNOSN)

Structural Principles of Tau Aggregation and Tau-Dependent Neurodegeneration

Tau is an unusual protein from several points of view: (1) Neurodegenerative diseases: Changes in Tau are early markers of AD and other "tauopathies" (e.g. FTD, Pick disease, PSP etc), (2) Neuronal cell biology: Tau is a brain-specific microtubule-associated protein (MAP), mostly confined to neuronal axons and implicated in neuronal differentiation, (3) Protein structure: Tau is the prototype of a "natively unfolded" or "intrinsically unstructured" protein, which does not require a defined structure for biological activity (in contrast to most "textbook" proteins with defined secondary and tertiary structure). We are interested in defining the interactions of Tau and the structural basis of its abnormal behavior in neurodegeneration. Tau is best known as an axonal protein that serves to stabilize microtubules, the tracks for long-haul traffic of vesicles and organelles in axons. As such, Tau interacts with tubulin (the building blocks of microtubules), motor proteins (kinesin, dynein), and several protein kinases and phosphatases that regulate these interactions. Malfunction of Tau (e.g. after hyperphosphorylation) can affect the stability of microtubules, interfere with motor-driven transport, and promote the pathological aggregation of Tau after detachment from microtubules. As a natively unfolded protein, Tau is not suitable for high resolution crystallography, however, the structure can be approached by spectroscopies (CD, fluorescence, FTIR, FRET) and NMR (solution and solid-state, collaboration with C. Griesinger, M. Zweckstetter, MPI Göttingen). The spectroscopic studies have revealed that Tau has "hotspots" for aggregation due to their tendency to form β-structure, and that Tau in solution has a "paperclip" folding where the N- and C-termini interact with the repeat domain. Both properties can be modified by phosphorylation at several sites. Knowledge of the β-forming hotspots enables one to design Tau molecules which favor or inhibit aggregation (pro- and anti-aggregant Tau). These variants now form the basis for designing cell- and animal models of tauopathy, and for screening inhibitors of Tau aggregation and other therapeutic agents (collab. B. Bulic, CAESAR). - Supported by MPG, DFG, VW Fnd, BMBF (KNDD), Metlife Fnd.

Dr. Eckhard Mandelkow

DZNE, German Center for Neurodegenerative Diseases, Bonn, Germany

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8th Floor

Neuroscience Center of Excellence Conference Room

more info zdavis@lsuhsc.edu