PL1

Deciphering Tau Neuropathology: From Silver Stain Toward a Near-atomic Resolution

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During the decades that followed Alois Alzheimer's 1906 and 1911 discoveries of argentophilic inclusions, now known as neurofibrillary tangles (NFT) and Pick bodies (PiB), many neurodegenerative diseases, characterized by similar inclusions, have emerged. Using the Bielschowsky method or other silver stains, it has been possible to study the neuroanatomical distribution of these inclusions, in sporadic and hereditary syndromes. Since the 1950s, the advent of electron microscopy (EM) has allowed to define a variety of pathologic fibrillary aggregates in neurons and glia. However, it has been the discovery of tau, in 1975, that has marked the beginning of a new era, during which significant progress in understanding neurodegeneration has occurred, along with the discovery of previously unrecognized diseases characterized by tau pathology. Since 1976, the Neuropathology Laboratory, at Indiana University (IU), has been at the forefront in deciphering diseases with neurofibrillary degeneration and tau pathology, not only through the study of forms of dominantly inherited AD, associated to novel APP, PSEN1, and PSEN2 mutations, but also through the discovery of tau pathology in Gerstmann-Sträussler-Scheinker disease and Prion Protein Cerebral Amyloid Angiopathy, two dominantly inherited prion protein amyloidoses. The role of tau pathology in neurodegeneration acquired a central position in 1998, when the discovery of mutations in the MAPT gene was key into revealing the phenotypic complexity of the cellular and molecular pathology in tauopathies. In these disorders, intracytoplasmic neuronal and glial tau inclusions derive from the aggregation of six tau isoforms or from the aggregation of isoforms with three or four repeats, resulting in diverse clinical and neuropathologic phenotypes. More recently, studies of NFT and PiB, using Cryo-EM, revealed, for the first time, the atomic structure of the tau filaments that form these inclusions. The molecular neuropathology of tau in the diseases discovered at IU will be presented in detail.

PL2

Structures of tau filaments from Alzheimer's and Pick's disease brains

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The ordered assembly of tau protein into abnormal filamentous inclusions underlies a large number of human neurodegenerative diseases. Tau filaments with distinct morphologies and isoform compositions characterise many of these diseases. Together with experimental studies, this has led to the suggestion that multiple molecular conformers of aggregated tau may exist. Electron cryo-microscopy can be used to determine the high-resolution structures of amyloid filaments from human brain. Paired helical and straight tau filaments of Alzheimer's disease are ultrastructural polymorphs. Each filament core is composed of two identical protofilaments extending from G273/304-E380 (in the numbering of the 441 amino acid isoform of human tau), which adopt a combined cross-β/β-helix structure. They comprise the end of the first or second repeat (R1 or R2), the whole of R3 and R4, as well as 12 amino acids after R4. By contrast, the ordered core of the narrow tau filaments of Pick's disease consists of a single protofilament extending from K254-F378 of three-repeat tau, which adopt a cross-β structure. It comprises the distal 21 amino acids of R1, all of R3 and R4, as well as 10 amino acids after R4. The wide tau filaments of Pick's disease, which are in the minority, consist of two protofilaments linked by the anti-parallel stacking of C322-S324. These findings show that filamentous tau protein can adopt distinct folds in different human neurodegenerative diseases, establishing the existence of multiple molecular conformers of aggregated tau.

PL3

Future of the Japanese Society of Neuropathology

Shigeo Murayama

President, the Japanese Society of Neuropathology

The Japanese Society of Neuropathology (JSNP) has been focusing on neurodegenerative disorders and is quite unique in the world. This may be quite helpful to establish brain bank network in Japan. We now succeed in building up high- quality brain bank consortium of neurodegenerative disorders. My first mission is to establish all Japan brain bank network to recruit brain donors of intractable neurological disorders.

The next step is to help consolidate brain banks of psychiatric disorders and, next, establish brain banks of pediatric and developmental neurological disorders.

We are starting the program of JSNP endorsed Board of Neuropathology after this meeting and one of the aim is to educate brain bank neuropathologists,

There are several unsolved problems.

1. How to cope with paradigm shift of brain tumor diagnosis.
2. How to collaborate with neuroscientists, especially in genomic research.
3. How to collaborate with forensic pathology.
4. How to collaborate with veterinary pathology.

We form ICN 2018 programs to answer these questions. Any comments are quite welcome.