



Project Leader **Masato Hasegawa** Dementia Research Project

## Prion-like propagation of tau, $\alpha$ -synuclein and TDP-43 in neurodegenerative diseases

Neurodegenerative diseases are characterized by progressive degeneration of subsets of neurons and gliosis. Many of the diseases are accompanied with intracellular amyloid-like protein pathologies, such as tau in Alzheimer's disease (AD),  $\alpha$ -synuclein in dementia with Lewy bodies (DLB) and TDP-43 in amyotrophic lateral sclerosis (ALS) and frontotemporal dementias (FTLD). Importantly, the distributions and spread of these proteins are closely correlated with clinical presentation and disease progression. However, little attention had been given to the questions of why these diseases are progressive, and why the pathologies spread to different brain regions during the course of the

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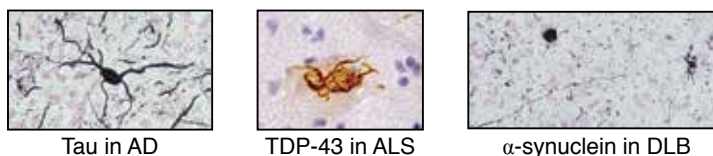
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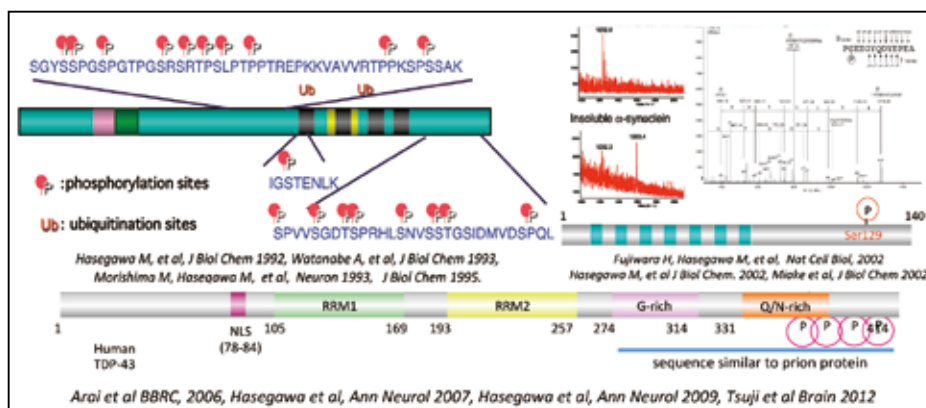
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**"Emerging evidence indicates that intracellular amyloid-like proteins have prion-like properties and propagate from cell to cell by converting normal proteins into abnormal forms.**

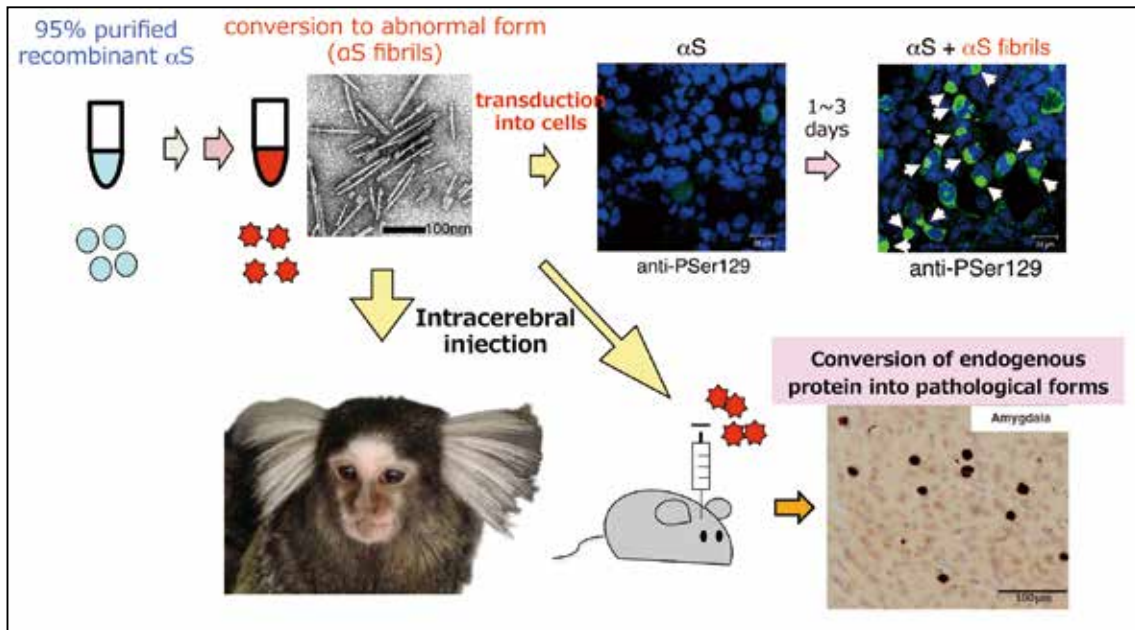
**We are trying to elucidate the molecular mechanisms of 'prion-like propagation of these proteins.'**

diseases. We have been investigating these intracellular abnormal proteins in brains of patients, proteinchemically using LC/MS/MS, immuno-histochemically with specific antibodies and ultrastructurally. And we found that all of these proteins are accumulated in brains of patients as fibrous or filamentous forms in hyperphosphorylated and partially ubiquitinated states.



Schematic diagrams of human tau,  $\alpha$ -synuclein and TDP-43.

To investigate the molecular mechanisms of aggregation of these proteins, we established seed-induced aggregation model which recapitulate the pathological protein aggregation in vitro, cultured cells and in brains of animals (mouse and marmoset) and proposed a hypothesis “prion-like propagation of these intracellular pathological proteins in brain”. These models are highly useful not only for clarifying the molecular mechanisms involved in the pathogenesis and progression of neurodegenerative diseases but also for the development of disease modifying drugs and therapy.



Senior Research Scientist **Takashi Nonaka**

### ***Molecular mechanisms of cell-to-cell propagation of aggregated proteins***

I'm studying molecular mechanisms of cell-to-cell propagation of aggregated proteins (tau,  $\alpha$ -synuclein and TDP-43) in neurodegenerative diseases. Also, I'm trying to make in vitro and in vivo models recapitulating abnormal features found in cells of brains of patients using cultured cells and mice. These models will contribute not only to a better understanding of the mechanisms involved in these diseases, but also to the development of novel therapeutic strategies.

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# Dementia Research