The way of tau

Neuroscientist and biochemist Dr Naruhiko Sahara gives an introduction to tau proteins, and explains why these unassuming molecules have been the focus of his long-term research interest over the last few years.

What initially spurred your interest in neuroscience and neurodegenerative diseases?

Perhaps because I am the youngest child in my family, the life and death of older people have become an important topic for me. My chosen academic discipline was protein biochemistry, and my original goal was to study disease mechanisms of the human cataract. I have always worked in the field of biochemical research and, over the course of my career, I have focused particularly on human diseases related to ageing.

Could you outline the main objectives of your research?

My research is largely focused on studying the mechanisms of Alzheimer’s disease. As an expert biochemist and molecular biologist, I have worked on discovering the mechanisms of disease pathology as well as the development of better diagnostics and therapeutics using in vitro and in vivo model systems.

As Senior Researcher and Assistant Director of the Neuromolecular Dynamics Team at the Molecular Imaging Centre, Japan, can you summarise the main research projects you are currently focusing on?

Our previous studies have successfully demonstrated that our novel radioligand is suitable for use in positron emission tomography (PET). Following on from this achievement, our current project aims to confirm the merits of our PET tracer for the diagnosis of Alzheimer’s disease and related neurodegenerative diseases. Furthermore, we hope to develop imaging agents for earlier tau-condition diagnosis.

In parallel, our other research aim is to develop imaging-based diagnostic procedures such as imaging biomarkers for brain protein ageing – a term to explain the dysfunction of proteins associated with neurodegenerative disease.

You are examining the mechanisms of Alzheimer’s disease, among other neurodegenerative diseases, by concentrating on different aspects of protein biochemistry and neurochemistry. What work is being conducted here at present?

At the National Institute of Radiological Sciences, Japan, we have multiple imaging systems for imaging the brains of small animals including mice, rats, marmosets, and macaques. Using certain animal models resembling human diseases, we have conducted neuroimaging studies on methods such as magnetic resonance imaging (MRI), PET and multiphoton microscopy. MRI and PET are non-invasive approaches to detect any abnormality of brain functions.

How do you aim to better facilitate collaboration between the basic neurochemistry and brain ageing research fields?

Currently, I am an investigator on a national research project called Brain Protein Aging and Dementia Control, which is supported by the Japanese Government. We aim to make novel insights and develop therapeutic tools for brain protein ageing. Within this project, researchers from basic and clinical fields of medicine get together and grow their networks. Experts in molecular biology, protein biochemistry, neuropathology, neurology and imaging are cooperating together and driving this new academic field.

For 10 years, your research has focused on tau protein dysfunction; what fundamental questions have you set out to answer here? Have you been able to provide answers to these questions to date?

In Alzheimer’s disease, neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein and neuronal cell loss coincide within the same brain regions. The progressively expanding anatomical distribution of NFTs is concomitant with growing brain dysfunction. Therefore, tau protein must have toxic effects in the neurodegenerative process. However, there is currently no clear way to identify toxic species of tau protein. To find these species, I have examined tau aggregation processes using several experimental systems including recombinant tau protein aggregation assays, cell culture systems, transgenic mouse models and extracted proteins from human autopsy brains.
New knowledge in neurodegeneration

A team of neurological and imaging scientists at the National Institute of Radiological Sciences in Japan has been responsible for the development of novel models and imaging methods to study the brain under disease conditions associated with neurodegeneration.

**AT A MOLECULAR**

level, microtubules are extremely important to life. Not only do they make up, along with microfilaments, a large proportion of the cytoskeleton, which gives cells their structure, but they are also integral to the movement of components within the cell and even to cell division. In a sense, microtubules are like roads; once they have been established, vesicles containing many kinds of proteins and molecules can travel along them, moving from one part of the cell to another.

Microtubules cannot accomplish these important goals alone. Although they can be comparatively large, sometimes achieving lengths of around 50 μm, microtubules are in fact made up of only two protein subunits – tubulin alpha and beta. In order to become stable over such great intracellular distances, these dimers rely on a range of microtubule-associated proteins, including tau proteins, which join to them and hold them steady. There are many forms of microtubule-associated proteins that prevail in different cell types – and tau proteins are associated exclusively with nerve cells.

**DISEASE CONDITIONS**

Tau proteins have been the subject of much study in recent years, partly because their operation has been linked with the onset of Alzheimer’s disease. Under normal conditions, tau is present predominantly in the axon of the nerve cell, and binds to the subunits of microtubules as they form. By binding to them, tau proteins make the growing tubule more stable, and help it to build up faster. In the nervous tissues of a patient with Alzheimer’s, however, the distribution of tau protein is rather different. Here, the protein accumulates abnormally – but it is hyperphosphorylated, meaning that intracellular signalling prevents it from functioning.

In such cases, the protein can no longer bind with microtubules, or perform its function in stabilising them. The structures therefore become fragile and are often subject to detachment and disintegration – a phenomenon that may be causative of the observable symptoms presented by Alzheimer’s patients.

**TAUOPATHY**

One group at the National Institute of Radiological Sciences (NIRS) in Japan is eager to get to the bottom of the role of tau proteins in neurodegenerative diseases. Led by Dr Naruhiko Sahara, the researchers have made much progress in recent years towards understanding this so-called ‘tauopathy’. “My goal is to investigate therapeutic interventions and understand the mechanisms of tau-induced neurodegenerative diseases, toxic tau species, tau oligomers, hyperphosphorylated tau proteins and the ageing process for tau proteins are all undefined terms,” Sahara explains. The work he carries out along with colleagues began some years ago with their development of a novel mouse model of tauopathy, and the decision to investigate – by subjecting the model to neuroimaging studies – whether this pathology led to white matter dysfunction. For Sahara, the results of these first-of-their-kind studies were intriguing enough to prompt further examination; it seemed that tauopathy could be detected early using magnetic resonance and diffusion tensor imaging, because its accumulation had an impact on the ultrastructure of the white matter.

These mouse models, which are unusual in that they overexpress human tau, provide a unique opportunity to get to grips with the protein and understand its role in disease. The protocol that Sahara has developed, which brings these murine models together with efficient imaging methods, is already being used as a standard both in academia and industry to elucidate tauopathy and propose new therapeutic tools and drug delivery systems.

Now, Sahara and his collaborators will push this work even further, seeking methods that can open up in vivo imaging and help researchers visualise neuropathology in living brains. “After 20 years’ experience in molecular neurochemical research, I now find myself working in neuroimaging,” he reflects. “It’s lucky that I could bring my neurodegenerative disease models with me!”

**ESTABLISHING A NOVEL IN VIVO BRAIN IMAGING SYSTEM FOR DETECTING TAU-INDUCED NEURODEGENERATION**

**OBJECTIVES**

- To use in vitro and in vivo model systems in order to discover the mechanisms of disease pathology and develop better diagnostics and therapeutics for Alzheimer’s disease and related neurodegenerative disorders
- To establish a novel research field to connect basic neurochemistry with brain ageing

**TEAM MEMBERS**

Dr Makoto Higuchi, Team leader • Dr Takashi Horiguchi, Dr Jun Maeda, Dr Bin JI, Dr Masahiro Maruyama, Senior researchers • Maiko Ono, Dr Anna Barron, Dr Shimojo Masafumi, Researchers • Takehara Minamihisamatsu, Sayuri Sasaki, Technical Staff • Kana Osawa, Assistant

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