Impact Objectives

- Study the molecular and cellular mechanisms of neural plasticity and factors such as neurotrophins and adult neurogenesis
- Investigate if it is possible to indicate whether cortical neurogenesis can be used to treat Alzheimer’s disease

Pioneering research into neurodegeneration

Associate Professor Koji Ohira discusses his research uncovering novel neural progenitor cells in the brains of adult mice and how they may be a key factor in neurodegenerative diseases

What path did you take to your current position?

I majored in biochemistry at the Kyoto Institute of Technology and was studying interferon-induced proteins. I completed my PhD in Neuroscience at the Kyoto University Graduate School, and I am now studying the molecular and cellular mechanisms of neural plasticity and factors such as neurotrophins and adult neurogenesis. I worked at the National Institute of Neuroscience, one of institutes of the Ministry of Health, Labor and Welfare, during my postdoctoral studies. Following that, I moved to Kyoto University School of Medicine as an Assistant Professor, and then to Fujita Health University. Since 2015, I have been conducting my research as an Associate Professor at Mukogawa Women’s University.

Can you talk a little about your work studying the factors affecting neurogenesis in the neocortex? What are you hoping to learn from this work?

Recent work has shown that antidepressant administration and learning have been found to promote cortical neurogenesis. At the same time, it seems that aging reduces cortical neurogenesis. In the preliminary experiments, it appears that cortical neurogenesis may be affected by chronic mild stress for three to six weeks. Other key factors, such as brain diseases, external environments, exercise and genes, are still largely unknown. In this project, we can clarify whether Alzheimer’s disease is one of the factors. In other words, it is possible to indicate whether cortical neurogenesis can be used to treat Alzheimer’s disease.

Who will ultimately benefit from this work?

The new production of neurons in the adult brain was almost unbelievable just 20 years ago. However, mainly by technological innovation in microscopy, it has become clear that neurons are produced in a few regions of the adult brain, such as the hippocampus and olfactory bulb. On the other hand, whether new neurons are produced in the cerebral cortex of adult mammals is still an active question. In this context, we found neural progenitors capable of producing new neurons in the adult cerebral cortex. However, so far, we have only found these cells in rodents and a few species of primates, and it is not known at all whether they exist in the human cerebral cortex. If the cells are found in humans, it becomes the first discovery of tissue stem/progenitor cells in the cerebral cortex of adult humans!

We are also looking to clarify the relationship between cortical neurogenesis and brain diseases, using the post-mortem brains of patients with neuropsychiatric diseases. We are particularly interested in Alzheimer’s disease. Population aging is becoming a problem in the world, especially in developed countries. Worldwide, around 50 million people have dementia, and there are nearly 10 million new cases every year. Alzheimer’s disease is the most common form of dementia and may contribute to between 60 and 70 per cent of cases. It is clearly a problem that there is no treatment for the disease. If any relationship exists, cortical neurogenesis becomes a new pathophysiology of Alzheimer’s disease. This in turn will become a light that illuminates the path towards a cure for many patients.

How have you overcome some of the challenges you have faced?

When we submitted the paper that discovered neural progenitors in the cerebral cortex, three reviewers gave us a fair amount of tough comments. However, without giving up, we carefully responded to the comments one by one, and the paper finally became accepted. From this experience, we have learned that it is important to carefully finish every detail.

Are you collaborating with any academic institutions or healthcare providers in your studies?

We are conducting joint research with Professor Katsuki Nakamura of Primate Research Institute of Kyoto University and Professor Tsuyoshi Miyakawa of Fujita Health University. The research group studies the effects of antidepressants on the primate brains.
Researchers at Mukogawa Women’s University have discovered neural progenitors in the cerebral cortex of mice that promise to shed light on neurodegeneration.

Neurodegenerative diseases represent one of the most significant health problems for developed countries in the 21st century. Generally, medicine is improving the quality of life long into old age. This has allowed life expectancies to rise and retirements to be more comfortable. However, there remain many untreatable age-related diseases. Neurodegenerative diseases are a huge proportion of these pathologies and are perhaps the most complex to deal with. Individuals can remain physically healthy in all aspects except for the brain. In diseases such as Alzheimer’s, this degradation starts with a loss of recent memory before worsening with disorientation, behavioural changes and the loss of bodily functions.

These diseases are chronic and progress at unpredictable rates. They are extremely distressing for the patient as the progression is confusing, degrading and extremely frustrating. Naturally, it is also distressing for the closest relatives who have to watch their loved one suffer from this terrible process. The disease also places a heavy financial and temporal burden on those who are the patient’s caregivers. Looking after a person suffering from a neurodegenerative disease quickly becomes a full-time job that requires special expertise and patience. The nature and burden of the disease makes finding solutions and ways to reverse its effects imperative. As one might expect, there is much research being conducted on this front, however, the disease pathologies are often varied and it is difficult to understand their exact cause. Thus far, there has been no satisfactory treatment for neurodegenerative diseases.

Amongst the researchers investigating neurodegenerative disorders is Associate Professor Koji Ohira of the Department of Food Science and Nutrition, Mukogawa Women’s University in Japan. He is pioneering work into understanding cortical neural progenitor cells in mice and is investigating their potential presence in humans. This work requires two key approaches – working closely with mouse models to understand the disease, progenitor cells and their interaction, as well as looking post-mortem at human brains in order to gain a clearer picture of the disease and whether or not neural progenitor cells exist in the cerebral cortex. ‘I believe that at least part of the disease’s pathology arises from the malfunctioning and/or degradation of neural stem cells capable of replacing damaged neurons,’ explains Ohira. ‘Our group has identified neural progenitor cells and neurogenesis in the cerebral cortex of adult mammalian brains, such as rodents and a few primates.’

CLOSE OBSERVATION
Ohira typically keeps things ‘simple’ when looking for novel cell types and conducting his mouse experiments. He and his team are experts in cell microscopy which entails dissection of the sample, preparation with various stains and an ability to identify rare morphologies and characteristics in a tangled web of neurons. They use a variety of intricate techniques to help them identify the neural progenitor cells. They then fix the brain samples and cut them into extremely thin slices. Typically, Ohira will use antibodies specific to the cells he is looking for and, through these, obtain an observable fluorescent signal. These samples were then imaged using confocal laser microscopy. Confocal microscopy can focus on different layers of the sample, take multiple pictures and reconstruct the image in three dimensions. With the right care and preparation, Ohira and his team were able to tease out the presence of neural progenitor cells within the adult cerebral cortex of mice.

In addition to being the first to identify cortical neural progenitor cells in adult mice, Ohira has also discovered a link to neurodegeneration. When he takes samples from older mice, they show a marked reduction in the levels of progenitor cells. As the mice age further, the levels of progenitors continue to drop.
Our group has identified neural progenitor cells and neurogenesis in the cerebral cortex of adult mammalian brains, such as rodents and a few primates.

This has important implications for neurodegeneration as it is likely that, if found, human cortex stem cells would show a similar drop off as age advances. “Working with mice also allows us the opportunity to experiment and introduce exogenous factors to help him illustrate the role of these neural progenitors,” highlights Ohira. “The aim of this work is firstly to identify the factors that cause the neural progenitors to activate and start the repair process. Secondly, and most pertinent for neurodegenerative disease, is to understand what causes the progenitors to disappear in the aging brain.

POTENTIAL MODEL

The discovery of neural progenitors in adult mice cortices is remarkable. For many decades, the prevailing wisdom was that, once the cortex stopped developing, no more new neurons could be made. “The model, therefore, was that the changing nature of the brain in old age was due to a loss of neurons over the years,” Ohira observes. However, this model didn’t really account for the slowness of this process nor explain rapid neurodegeneration in diseases such as Alzheimer’s. “The presence of neural progenitors suggests that there is a much higher rate of repair and maintenance than previously thought.” Crucially, it helps to explain the severe pathology of neurodegeneration. It seems highly probable that progenitors are being lost through some factor – likely a mix of genetics and exogenous stressors.

Before these hypotheses can be tested, Ohira must first prove the existence of progenitors in humans. This is a tricky process for two key reasons. Firstly, obtaining brain samples relies on post-mortem donations. These are likely to heavily skew towards the aged and provide an inconsistent resource. Secondly, the human cerebral cortex is many times larger than in the mouse. This means that many more sections must be prepared, thousands more images taken, and much time spent trawling through the resulting data. Despite these obstacles, Ohira remains hopeful of their discovery, especially as primates have also been shown to have the requisite cells.

Whilst the search for progenitors in the adult human cortex continues, Ohira is also following other avenues of research. He is beginning to expand his investigations to include other mental disorders. Particularly, he is looking at depression and its effects on cortex structure. “For this research we will start by screening the effects of nutrients that show antidepressant properties based on behavioural indicators of model animals with depression,” Ohira says. From this, he should be able to conduct similar experiments as before, image the brain at different stages of the disease and different ages. “Our hypothesis is that neural progenitors may have a role to play in depression and be a key point of interaction for drugs with antidepressant effects.”

HALTING DEGENERATION

Ohira’s work is breaking new ground in discovering novel progenitors in the adult cortex and understanding their pathology during aging. The presence of these progenitors in mice and primates changes how we comprehend the brain. His work will form part of the basis of our understanding of maintenance and aging in the cerebral cortex. Looking further ahead, his findings point towards methods of preventing the rapid neurodegeneration in Alzheimer’s and other forms of dementia. In addition, it is likely that cortical neural progenitors are also a factor in other mental and brain diseases. Ohira and his team should be able to guide the way towards solving many of these poorly understood pathologies.