

Impact Objectives

- Explore the underlying cellular and molecular causes of the Chronic Kidney Disease (CKD)
- Investigate the potential to develop a drug that inhibits the development or progression of CKD

A broad approach to kidney disease

Professor Reiko Inagi discusses her work and passion on tackling chronic kidney disease at an organ, cellular and molecular level



What type of research is being carried out at the Division of Chronic Kidney Disease Pathophysiology, the University of

Tokyo Graduate School of Medicine? What is the impact of this work and who will ultimately benefit from your research?

We are performing studies about the pathophysiology of organelle stress such as endoplasmic reticulum (ER) stress and mitochondrial stress, especially under hypoxia, oxidative stress or metabolic stress condition, all of which accelerate the development and progression of chronic kidney disease (CKD). Among CKD, diabetic kidney disease (DKD) is the leading cause of end-stage kidney disease (ESKD), and we are also studying the pathophysiology of DKD utilising omics approaches. These studies will give us new insights into the pathophysiology of CKD and DKD, leading

to the development of novel therapeutic strategies of a broad range of kidney disease, a growing global problem.

You are working to develop more effective CKD preventative and therapeutic strategies. How do you envisage your findings will be applied to healthcare settings?

We are elucidating the pathophysiology of CKD and finding surrogate markers and novel therapeutic targets. Our findings will be translated into real-world applications for healthy longevity with a healthy kidney.

You work with a number of international students. Can you talk about the value of this to both your studies and the students, as well as the importance of supporting early stage researchers?

It is important to support early stage researchers because they are the future of science. They are the ones who will solve the problems that we cannot answer at

this moment. To work and discuss with international students or visiting researchers stimulates our projects through the diverse points of view that give us a new insight.

How will the knowledge you have gathered be shared with other academic institutions and healthcare organisations?

I publish our works in peer-reviewed journals and give talks at scientific meetings. Those at other academic institutions and healthcare organisations share our updated finding by reading our papers and listening to my lectures.

What does the future hold for your research? What would you like to be working on in the near future?

I would like to be working on developing new surrogate markers and drugs for the prevention of kidney disease, especially CKD and DKD. ●



A new response to an old problem

Researchers in the Division of Chronic Kidney Disease Pathophysiology, the University of Tokyo Graduate School of Medicine, are tackling the growing problem of chronic kidney disease through a comprehensive omics approach

Chronic diseases are quickly outstripping other reasons for sources of morbidity in developed societies. Many developed nations have to deal with the modern problem of an ageing population and large sections of the population are now growing old.

Medical care for the aged has improved dramatically over this time period, however, many fundamental aspects of ageing are not entirely understood. Put quite simply, it is not yet clear what causes ageing and why it has such a dramatic effect on the homeostasis and longevity of the body. Along with the problem of ageing, these same nations are also those that have the highest rates of chronic diseases, such as lifestyle-related diseases, including diabetes, cardiovascular disease and hypertension. These two factors together mean that diseases and disorders that result from the breakdown of homeostatic pathways are becoming ever more important in developed countries.

UNDERLYING PATHOGENIC MECHANISMS

Chronic kidney disease (CKD) is the most neglected disorder that is becoming extremely prevalent. An estimated 850 million people are affected by kidney disease globally, representing one in 10 of the global population. The scale of the disease is clearly huge. The disease itself often does not present with many symptoms, however, if allowed to progress, it can lead to outright kidney failure or other complications such as heart attack, arteriosclerosis and stroke. CKD is also a huge economic burden for societies. There is strong evidence that CKD is a consequence of other long-term chronic diseases such as diabetes.

However, the underlying cellular and molecular causes of the CKD are not well-established. Professor Reiko Inagi, chief of the Division of Chronic Kidney Disease Pathophysiology, the University of Tokyo Graduate School of Medicine, is investigating the underlying cellular and molecular mechanisms behind CKD. Understanding these mechanisms is a crucial step towards developing a novel drug that may be able to inhibit the disease at a molecular level.

Inagi, along with her collaborator Professor Masaomi Nangaku of the Division of Nephrology and Endocrinology, the University of Tokyo Graduate School of Medicine and a team of young researchers, is approaching the investigation of CKD from various new angles. 'We have a myriad of different projects including: identifying the mechanism of destruction of adaptive signals to various stresses such as oxidative stress, hypoxia and metabolic disorders in CKD; understanding the pathophysiology of organelle stress including endoplasmic reticulum (ER) stress or mitochondrial stress and organelle crosstalk; clarifying the mechanism of functional change in renal erythropoietin (EPO)-producing cells along with the mechanisms of CKD progression; identifying factors in the exacerbation of CKD in patients with diabetes; and using the findings obtained to establish new CKD treatment strategies,' explains Inagi. 'This many-angled approach makes for a clearer overall picture of the biology and biochemistry of the disease.' This, in turn, maximises the Division's ability to find treatments and propose viable therapeutic solutions.

CHATTERING ORGANELLES

Previous work from Inagi's team has demonstrated a novel link between two key cellular organelles that plays an important role in the progression of CKD. The ER is a cellular structure that is responsible for protein maturation through the regulation of their correct synthesis, folding and degradation. Through this, it has a key function in maintaining the quality of proteins that is essential for normal cell function. 'We have previously demonstrated that the ER is also responsible for communicating with the mitochondria to control the mitochondrial structure and function,' observes Inagi. 'Mitochondria are the energy factories of the cell, producing the majority of the cell's adenosine triphosphate (ATP) molecule, used as an energy source by all life. Kidneys are extremely energy-intensive and therefore their cells, especially proximal tubular cells, are rich in mitochondria.' Inagi believes that the breakdown in communications between the ER and the mitochondria is a crucial factor in the progression of CKD.

Inagi's research has shown that the unfolded protein response (UPR) pathway plays an important role in the crosstalk between the ER and the mitochondria. The UPR is a stress response that detects and tries to solve problems involving deterioration of ER function, ER stress. 'First it tries to solve the problem and, if it is unable to do so, it will lead the cell to kill itself through apoptosis,' she highlights. Inagi and her team have reported that the activation of maladaptive UPR pathway causes the development/progression of CKD and DKD as well as an ageing of the kidney. Furthermore, they have found that ►



the maladaptive UPR pathway is at least in part caused by an accumulation of metabolic wastes (e.g. uremic toxins) and that this may be causing disruption in the mitochondria and thus energy production. They are now working towards identifying the specific molecules involved in the UPR that may be part of this cross-communication between organelles.

A GLOBAL APPROACH

In order to follow up these investigations, Inagi and her team are utilising the power of transcriptomics and metabolomics. The transcriptome is made up of all the genes currently being expressed. This is usually measured by proxy through the mRNA levels of each gene. 'By analysing the transcriptome at different times and under different pathogenic conditions, we will be able to pick out the key genes involved in CKD and ER-mitochondrial crosstalk,' notes Inagi. Metabolomics is the collection of metabolites in the cell (or organ) at a given time. Metabolites are the waste products from energy production and cell survival. The concentrations at which they are present give crucial indications of the metabolic state of the cells being analysed. This metabolic state is influenced by the health of the cell and should therefore help build a picture of both healthy renal cells and those in the throes of CKD. 'Combining the data from these two will provide a fascinating insight into the important proteins and pathways involved and pick out specific proteins and molecules involved,' she says.

For the clinical application of the molecular and cellular biological findings based on omics studies, the researchers are utilising mouse and rat kidney disease models to perform the transcriptome and metabolome analyses. Specifically, they are looking at the acute and chronic kidney disease models with or without metabolic disorder (e.g., diabetes and dyslipidaemia). Her position at the university hospital also allows her

group easy access to human biomaterials, allowing translation of their research to bed-side utilisation. They are investigating both glomeruli and renal tubules to evaluate their crosstalk from the point of view of a decline in kidney function and renal fibrosis. The metabolomics of these regions will look at the carbohydrate, lipid and amino acid metabolic profiles and link these to the transcriptomics which should show varying levels of gene expression in range of related genes. Inagi explains the power of these experiments beyond just understanding pathophysiology of organelle crosstalk. 'By using kidney disease model animals we are studying not only the importance of the link between organelle crosstalk and kidney disease, but also the impact of organelle crosstalk on the maintenance of cellular homeostasis.'

BROAD IMPACT

The work of the Division of Chronic Kidney Disease Pathophysiology and their collaborators has the potential to impact the millions across the globe who suffer from CKD. This comes at a particularly crucial juncture where the populations of developed countries are ageing and becoming extremely susceptible to chronic diseases. 'We will develop and target a specific molecule involved in CKD, and we will halt the progression of the disease and increase the quality of life of many sufferers,' promises Inagi. In addition, their findings will also be important in examining other kidney diseases and may help in finding solutions to those as well. Inagi's valuable research projects are well-known worldwide, offering her numerous occasions to give invited lectures at international academic conferences. Inagi has a number of collaborators in the USA, Europe, and Asia-Pacific regions, allowing her to tackle the problems from a diverse and international point of view. In short, the impact of Inagi and her collaborators' work could be far-reaching and essential to help tackle these challenges. ●

Project Insights

FUNDING

- Japan Society for the Promotion of Science Grants-in-Aid for Scientific Research
- The research grant from Kyowa Kirin Co. Ltd.

COLLABORATORS

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BIO

Professor Reiko Inagi is the Division Chief of Chronic Kidney Disease Pathophysiology, the University of Tokyo Graduate School of Medicine. She earned her PhD from Nagoya University Graduate School of Medicine (1990). She became an assistant professor at Osaka University School of Medicine (1991-1998), moved to Tokai University School of Medicine as a lecturer and began her studies in molecular nephrology. Inagi received her "Kimoto Award" from the Japanese Society for Dialysis Therapy (2003). Inagi is a councillor/secretary of Japanese Society of Nephrology and International Maillard Reaction Society, an associate editor of *Clinical and Experimental Pharmacology and Physiology*, and Editorial board of *American Journal of Physiology-Renal Physiology* and *Kidney International*.

