Division of Organogenesis

Kidney Development

The kidney: among the most complex of all organs Carving out a new path toward treating kidney failure By clarifying developmental mechanisms and examining the possibilities of regeneration

Among all the internal organs, the kidney is acknowledged as being particularly complex.
At present, decline in kidney function cannot be repaired.
Professor Ryuichi Nishinakamura is working on establishing the mechanisms of kidney development,
with the hope that his research will one day help make kidney regeneration possible,
thereby opening the way for new treatments of kidney failure.

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Profile

Graduated from the Faculty of Medicine, The University of Tokyo. He then worked as a physician of internal medicine for four years, at The University of Tokyo Hospital and Jichi Medical University Hospital, among others.
In 1991, he began research at The Institute of Medical Science at The University of Tokyo.
In 1993, he became a research fellow at DNAX Research Institute in the United States.
In 1996, he completed a doctoral degree at the Graduate School of Medicine, The University of Tokyo.
He then took up a position as a research assistant at The Institute of Medical Science at The University of Tokyo, and then a visiting associate professor at the same institute.
In 2004, he joined the Institute of Molecular Embryology and Genetics Center at Kumamoto University as a professor, and in 2010 the Deputy Director of the Institute.

References

- Fujimoto, Y., Tanaka, S.S., Yamaguchi, Y.L., Kobayashi, H., Kuroki, S., Tachibana, M., Shinomura, M., Kanai, Y., Morohashi, K., Kawakami, K., and Nishinakamura, R. Homeoprotein Six1 and Six4 regulate male sex determination and mouse gonadal development. Dev. Cell 26: 416-430, 2013.
- Sakaguchi, M., Sharmin, S., Taguchi, A., Ohmori, T., Fujimura, S., Abe, T., Kiyonari, H., Komatsu, Y., Mishina, Y., Asashima, M., Araki, E., and Nishinakamura, R. The phosphatase Dullard negatively regulates BMP signalling and is essential for nephron maintenance after birth. Nat. Commun. 4: 1398, 2013.
- Uchiyama, Y., Sakaguchi, M., Terabayashi, T., Inenaga, T., Inoue, S., Kobayashi, C., Oshima, N., Kiyonari, H., Nakagata, N., Sato, Y., Sekiguchi, K., Miki, H., Araki, E., Fujimura, S., Tanaka, S.S., and Nishinakamura, R. Kif26b, a kinesin family gene, regulates adhesion of the embryonic kidney mesenchyme. Proc. Natl. Acad. Sci. USA 107: 9240-9245, 2010.
- Fujimura, S., Jiang, Q., Kobayashi, C., and Nishinakamura, R. Notch2 activation in the embryonic kidney depletes nephron progenitors. J. Am. Soc. Nephrol. 21: 803-810, 2010.

Aiming for kidney regeneration using Sall1 as an indicator

The kidney is a very complex organ, which is perhaps why there are so few researchers working on its developmental mechanisms with the intention of feeding research output into developing regenerative therapies. "To be honest, when I first started my research in kidney development, I was not really sure what to do. I was fumbling around, without clear direction," says Dr. Nishinakamura, recalling his early research. "I spent about three years working with frog models, trying to identify genes that affect development. Finally, I was able to identify the Sall1 gene, through a series of experiments using knockout mouse models". This gene, which had been so hard to find, plays a vital role in kidney development, to the extent that deficiency in Sall1 will cause kidney agenesis.

Continuing with his research, Dr. Nishinakamura was able to determine that the kidney develops from several different types of cell clusters, and that kidney development shares aspects similar to stem cell biology. To date, it has been established that progenitor cells, the building blocks of the kidney, express Sall1 very strongly. Genes other than Sall1 have also been identified, and have subsequently been demonstrated as important to kidney development. "By examining the mechanisms of kidney development, one by one, and using Sall1 as an indicator, I hope that we will be able to induce kidney progenitor cells from embryonic stem and induced pluripotent stem cells and use those to further our research into kidney regeneration," says Dr. Nishinakamura.

Discovering the gene vital to kidney growth

Dr. Nishinakamura proved the importance of Sall1 beyond doubt, but the genes functioning up and downstream of Sall1 remain undiscovered, as do the genes that are the target of the regulatory activity of Sall1. Recently, the team at Dr. Nishinakamura's laboratory has discovered that a gene named Kif26b is directly targeted by Sall1. The absence of Kif26b results, similarly, in kidney agenesis. "This is the result of seven years of research. It is another step towards realizing kidney regeneration."

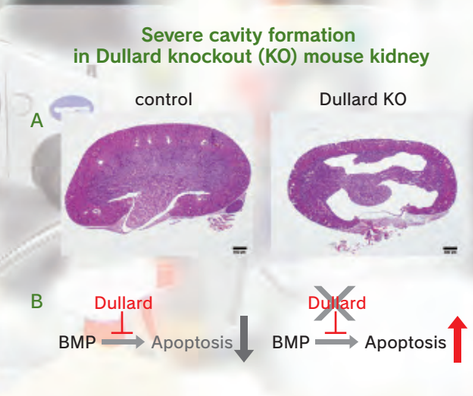
The team has also discovered a gene named Dullard. "In a Dullard-knockout mouse study, we were able to show that while the embryonic mice are healthy, as soon as they are born cell death starts to occur in the kidney causing a cavity in the organ, and lethality within eight weeks after birth. The conclusion we can draw from this is that while Sall1 is vital for kidney formation, Dullard has an important role to play in maintaining the kidney," says Dr. Nishinakamura. The results of these findings were published in the Nature Communications on January 29, 2013. "Dullard works to regulate the signaling of BMP, a factor that causes cell death. We further established that the condition of Dullard-knockout mice could be improved through the injection of drugs designed to constrain BMP signaling." If the mechanisms behind the maintenance and growth of the kidney can be uncovered, this knowledge will shed light on the processes that cause kidney failure in young children, as well as other kidney-related conditions.

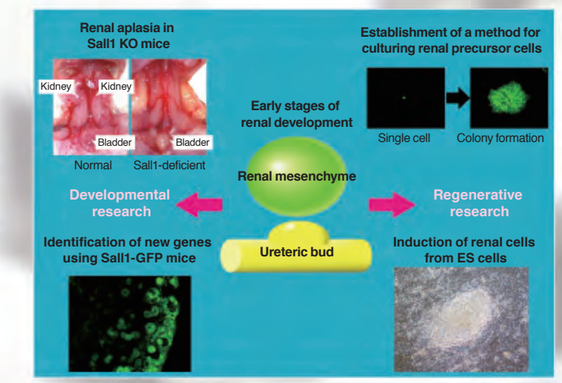
Do not be afraid of failure, and face up the challenge

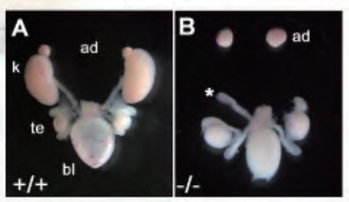
The kidney has a vital role to play in the functioning of the body: it removes waste material from the body as urine and regulates the volume of water within the body. Severe decline in kidney function will have a fatal effect on maintaining life. At present, the main treatment in place for kidney failure is artificial dialysis. But this option does nothing to recover the function of the damaged kidneys.

Looking at the potential for organ regeneration, the kidney is thought to present a particular challenge. Even if we succeed in explaining and understanding the mechanisms of kidney development and maintenance, it will doubtless be a long time before any such findings may be translated into clinical applications. "It is exactly the challenging nature of this research, and this organ, that has meant few laboratories have studied kidney development to the extent that we do. This allows me and my team to undertake highly original research," says Dr. Nishinakamura, clearly passionate about his subject.

"My young researchers are not afraid of testing their ideas, and indeed they have produced some great results. Nature is so much greater than human knowledge and understanding. That is what makes it so fascinating. If we are to have any hope to uncover nature's secrets with science, we need to push forward, without being afraid of failure. I urge you to keep asking yourself whether you are living up to the expectations of the patients whose lives could be improved by your research. I would like you to keep your motivation levels high and remain very committed to your research."







Teaching Staff

Assistant Professor

Satomi S. Tanaka

My research focuses on the formation and differentiation of mouse germline cells, specifically how next-generation germline cells are produced, and how they are different from stem cells and somatic cells. My desire to answer these questions is what drives my research. I am also studying the structure of male and female sex differences, which form the basis of sexual reproduction.