【Grant-in-Aid for Scientific Research (S)】

Broad Section I

Title of Project : Reconstitution of the higher-order structure of the human kidney based on stromal progenitor induction

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Keyword : Kidney development, iPS cell, stromal progenitor

【Purpose and Background of the Research】

Although 330,000 patients are under dialysis due to kidney failure and the annual medical cost reaches 1.5 trillion yen, no curative treatment is available and there is a shortage of donors for kidney transplantation. The kidney is formed by the interaction of three types of progenitors: nephron progenitors, ureteric buds, and stromal progenitors. We have previously reported in vitro induction methods of nephron progenitors and ureteric buds from mouse ES cells and human iPS cells (i.e. kidney organoids).

In this project, we will develop a method to induce the third progenitor, stromal progenitor, and combine it with the first two to reconstruct the higher-order structure of the kidney, in which functional units are arranged around branching structures. We will accomplish this in humans by elucidating the species differences between mice and humans. In addition, we aim to generate organoids with the function of producing and excreting urine by securing blood flow and urinary tracts through transplantation.

【Research Methods】

We have performed single-cell RNA sequencing (scRNA-seq) of mouse kidneys from various developmental stages and have identified markers and signaling molecules that are expressed in subpopulations of the stroma at each stage. Based on this information, we will induce stromal progenitors from mouse ES cells. By combining the stromal progenitors with ES cell-derived nephron progenitors and ureteric buds, we will construct a kidney higher-order structure that is entirely derived from ES cells.

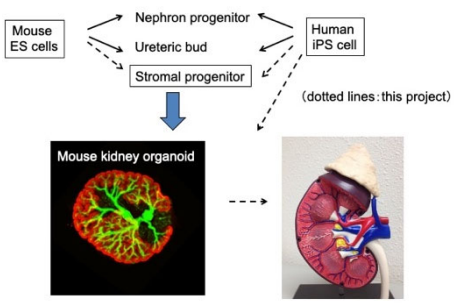

Figure 1. Reconstitution of the higher-order structure of the human kidney

Next, we will establish the induction method of stromal progenitors from human iPS cells. Because the cell types and gene expression of the human embryonic kidney are being elucidated, we will use this information as the basis for the induction of progenitors that differentiate into the intra-renal stroma. By combining these cells with human iPS cell-derived nephron progenitors and ureteric buds, we will construct the higher-order structure of the human kidney. Furthermore, we will develop a method to induce another type of stromal progenitor that differentiates into stromal cells around the ureter. Eventually, we will reconstruct the higher-order structure of the kidney equipped with the ureter so that the transplanted kidney organoids will acquire the basic function of the kidney, which is to make and drain urine.

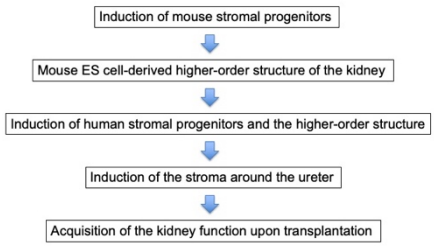

Figure 2. Reconstitution of the higher-order structure based on stromal progenitor induction

【Expected Research Achievements and Scientific Significance】

We have already succeeded in recapitulating the initial disease state of congenital nephrotic syndrome and polycystic kidney disease using patient-derived iPS cells (Stem Cell Reports 2018, J Am Soc Nephrol 2020). However, the current organoids are nephron only or ureteric bud only and immature. This project is expected to provide a basis for drug discovery by recapitulating and elucidating the later disease state of hereditary kidney diseases. In addition, if the basic function of the kidney can be acquired, it will be a breakthrough for future transplantation medicine.

【Publications Relevant to the Project】

・Taguchi A and Nishinakamura R. Higher-order kidney organogenesis from pluripotent stem cells. **Cell Stem Cell** 21: 730-746, 2017.
・Taguchi A, Kaku Y, Ohmori T, Sharmin S, Ogawa M, Sasaki H, and Nishinakamura R. Redefining the in vivo origin of metanephric nephron progenitors enables generation of complex kidney structures from pluripotent stem cells. **Cell Stem Cell** 14: 53-67, 2014.

【Homepage Address and Other Contact Information】

http://www.imeg.kumamoto-u.ac.jp/bunya_top/kidney_development