Novel therapeutic strategy for kidney and endocrine diseases using iPS cell technology

Hirofumi Hitomi¹

¹Dept. iPS Stem Cell Regenerative Medicine, Kansai Medical Univ.

The differentiation of induced pluripotent stem cells (iPSCs), which have unlimited self-renewal capability and the potential to differentiate into any cell type in the body, provides promising cell sources for regenerative medicine. The somatic cell types differentiated from these stem cells have the potential for clinical applications, including cell therapy and drug screening. In this symposium, I will briefly summarize our novel therapeutic strategy for kidney and endocrine diseases using iPS cell technology.

Firstly, I will present our recent findings about cell therapy for renal anemia. The production of erythropoietin (EPO), a principal hormone for the hematopoietic system, by the kidneys is reduced in patients with chronic kidney disease (CKD), eventually resulting in severe anemia. Although recombinant human EPO treatment improves anemia in patients with CKD, returning to full red blood cell production without fluctuations does not always occur. Although vigorous efforts have been made to generate multiple somatic cell types from stem cells, the directed differentiation of EPO-producing cells (EPO cells) from iPSCs has not yet been achieved. Recently, we established a method to generate EPO-producing cells from human iPSCs (hiPSCs) by modifying previously reported hepatic differentiation protocols. These cells showed increased EPO expression and secretion in response to low oxygen conditions. The EPO protein secreted from hiPSC-derived EPO-producing (hiPSC-EPO) cells induced the erythropoietic differentiation of human umbilical cord blood progenitor cells *in vitro*. Furthermore, transplantation of hiPSC-EPO cells into mice with CKD induced by adenine treatment improved renal anemia. Thus, hiPSC-EPO cells may be a useful tool for clarifying the mechanisms of EPO production and may be useful as a therapeutic strategy for treating renal anemia.

Secondly, I will mention about drug screening and evaluation for renal anemia. It has been reported that EPO production is regulated by oxygen concentrations through hypoxia-inducible factors and their regulators, prolyl hydroxylase domain-containing enzymes (PHDs). Several PHD inhibitors are currently in clinical trials for treatment of renal anemia. Interestingly, our recent findings showed that a PHD inhibitor augmented EPO production only in hiPSC-EPO cells, but not HepG2 cells, which are an immortalized human hepatoma cell line and are widely used to investigate EPO production. These findings suggest that hiPSC-EPO cells may provide a good model for screening PHD inhibitors for their effects on renal anemia.

Finally, I will brief summarize recent topics about cell therapy for endocrine disease using iPS cell technology.