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Research review paper

Stem cell-derived kidney cells and organoids: Recent breakthroughs and emerging applications

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ABSTRACT

The global rise in the numbers of kidney patients and the shortage in transplantable organs have led to an increasing interest in kidney-specific regenerative therapies, renal disease modelling and bioartificial kidneys. Sources for large quantities of high-quality renal cells and tissues would be required, also for applications in *in vitro* platforms for compound safety and efficacy screening. Stem cell-based approaches for the generation of renal-like cells and tissues would be most attractive, but such methods were not available until recently. This situation has drastically changed since 2013, and various protocols for the generation of renal-like cells and precursors from pluripotent stem cells (PSC) have been established. The most recent breakthroughs were related to the establishment of various protocols for the generation of PSC-derived kidney organoids. In combination with recent advances in genome editing, bioprinting and the establishment of predictive renal screening platforms this results in exciting new possibilities. This review will give a comprehensive overview over current PSC-based protocols for the generation of renal-like cells, precursors and organoids, and their current and potential applications in regenerative medicine, compound screening, disease modelling and bioartificial organs.

Contents

Abbreviations: AA, activin A; ADPKD, autosomal dominant polycystic kidney disease; AKI, acute kidney injury; AQP, aquaporin; ARPKD, autosomal recessive polycystic kidney disease; BMP, bone morphogenetic protein; CD, collecting duct; CDH1/ECAD, cadherin 1/E-cadherin; CDH2/NCAD, cadherin 2/N-cadherin; CHIR, CHIR99021; CITED, Cbp/p300-interacting transactivator with Glu/Asp-rich carboxy-terminal domain; CXCL, C-X-C motif chemokine ligand; DT, distal tubule; DTC, distal tubular cells; EB, embryoid bodies; ECM, extracellular matrix; ESRD, end stage renal disease; EOMES, eomesodermin; Ep, epiblast; EYA, EYA transcriptional coactivator and phosphatase; FGF, fibroblast growth factor; GATA, GATA binding protein; GDNF, glial cell derived neurotrophic factor; GFP, green fluorescent protein; GLUT, glucose transporter; HCS, high-content screening; hESC, human embryonic stem cell; HFM, hollow fiber membrane; HGF, hepatocyte growth factor; hiPSC, human induced pluripotent stem cell; HOX, homeobox; HPTC, human primary renal proximal tubular cells; HUVEC, human umbilical vein endothelial cells; IL, interleukin; IM, intermediate mesoderm; LHX, LIM homeobox; LPS, late primitive streak; LRP, LDL receptor related protein; LTL, *Lotus tetragonolobus* lectin; ME, mesendoderm; MEF-CM, mouse embryonic fibroblast-conditioned hESC medium; mESC, murine embryonic stem cell; MIXL, mix paired-like homeobox; MM, metanephric mesenchyme; MNP, metanephric nephron progenitor; MRP, multidrug resistance protein; NKC, neonatal kidney cells; NM, nascent mesoderm; NPHS1, nephrin; NPHS2, podocin; OSR, Odd-skipped related transcription factor; PA, pretubular aggregate; PAX, paired box; PECAM1/CD31, platelet and endothelial cell adhesion molecule 1; PIM, posterior intermediate mesoderm; PKD, polycystic kidney disease; PNM, posterior nascent mesoderm; POD, podocyte; PODXL, podocalyxin like; PS, primitive streak; PSC, pluripotent stem cells; PT, proximal tubule; PTC, proximal tubular cell; qPCR, quantitative real-time reverse transcription polymerase chain reaction; QSAR, quantitative structure-activity relationship; RA, retinoic acid; REGM, renal epithelial cell growth medium; RET, ret proto-oncogene; RV, renal vesicle; SALL, spalt like transcription factor; SGLT, sodium/glucose cotransporter; SIX, SIX homeobox; SLC12A1, solute carrier family 12 member 1; SOX, SRY-box; SYNPO, synaptopodin; T, brachyury; TC, tubular cell; UB, ureteric bud; UE, ureteric epithelium; UMOD, uromodulin; US EPA, United States Environmental Protection Agency; VEGF, vascular endothelial growth factor; VitD3, vitamin D3; WT, Wilms' tumor; W3, Wnt3a; 3D, three-dimensional.

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1. Introduction

Kidney tissue and renal cells are required for applications in compound efficacy and safety screening, regenerative medicine, bioartificial kidneys and disease modelling. A major hurdle is the availability of functional human renal cells and tissue (Jansen et al., 2014; Tasnim et al., 2010; Tiong et al., 2014). Stem cell-based approaches are attractive for addressing this problem. However, whereas approaches for the directed differentiation of stem cells into tissue-specific cell types had been well established with respect to various other organs and tissues, such as liver, heart or cartilage, nothing comparable was available for the kidney.

This situation started to change in 2012, when a protocol was established for the differentiation of human induced pluripotent stem cells (hiPSC) into renal podocyte-like cells (Song et al., 2012). Briefly afterwards in 2013, a race started on the differentiation of pluripotent stem cells (PSC) into different renal-like cell types and precursor-like cells of the renal lineage, and various protocols were published (Araoka et al., 2014; Kandasamy et al., 2015; Kang and Han, 2014; Lam et al., 2014; Mae et al., 2013; Narayanan et al., 2013; Taguchi et al., 2014; Takasato et al., 2014; Xia et al., 2013). In parallel, first methods for applications of such cells were established (Kandasamy et al., 2015; Li et al., 2014; Toyohara et al., 2015). The race continues and focuses currently on the generation of self-organizing kidney organoids (Freedman et al., 2015; Morizane et al., 2015; Takasato et al., 2015). Thus, amazing progress has been made during the last four years and exciting opportunities become available. Here, we will review these exciting developments.

Before we go into the details of current PSC-based approaches, we will briefly summarize background information on the kidney and its development. The kidney is essential for the clearance of xenobiotics and metabolic waste from the body, is indispensable for volume, electrolyte and pH homeostasis, and has also endocrinologic functions (Brenner, 2008; Fraser and Kodicek, 1970; Wilson et al., 2004). For instance, the renal interstitium contains specialized cells producing renin, which is part of the renin-angiotensin-aldosterone hormone system that regulates blood volume and blood pressure. Specialized interstitial fibroblasts produce about 90% of the body's erythropoietin, which controls red blood cell production (Kaissling and Le Hir, 2008; Zeisberg and Kalluri, 2015).

The functional unit of the kidney, which is essential for most other renal functions, is the nephron. The average nephron number per kidney is ~1 million, but there are substantial individual differences (Bertram et al., 2011). The nephron consists of the glomerulus, where filtration of the blood occurs, and the renal tubule, into which the glomerular filtrate flows (Scott and Quaggin, 2015). The renal proximal tubule (PT) is next to the glomerulus. The loop of Henle connects the PT with the distal tubule (DT), which leads into the collecting duct (CD; Fig. 1). The CD is not part of the nephron, and the branched CD tree connects the nephrons with the ureter (Brenner, 2008).

Glomeruli contain a tuft of capillaries lined by the glomerular filtration barrier, which consists of specialized endothelial cells, a basal lamina and the glomerular podocytes. Podocytes have a special morphology, and their foot projections wrap around the capillary walls and form a slit diaphragm, which is part of the glomerular filtration barrier (Reiser and Altintas, 2016; Scott and Quaggin, 2015).

The glomerular filtrate flows first into the PT, which is lined by the proximal tubular cells (PTC). PTC have manifold functions. For instance, they control the pH of blood and urine and reabsorb most of the water, glucose, peptides and proteins from the glomerular filtrate (Brenner, 2008; Curthoys and Moe, 2014). They are important for electrolyte and mineral homeostasis and produce the most active form of vitamin D (Brenner, 2008; Curthoys and Moe, 2014; Fraser and Kodicek, 1970). They also make major contributions to the clearance of metabolic

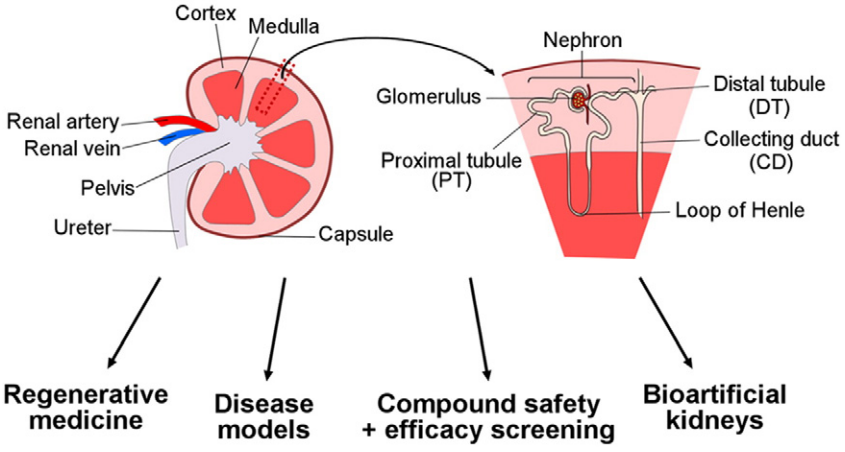

Fig. 1. Human kidney and nephron structure. The schematic drawing shows a cross-section of a human kidney (left). The enlargement (right) displays a nephron with a CD. The different parts of the kidney and nephron are indicated. At the bottom, the main areas of applications for stem cell-derived renal-like cells, precursors or organoids are indicated.