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In vitro models in studying nephropharmacology

Kidney-on-a-chip technology for renal proximal tubule tissue reconstruction

Tom T.G. Nieskens, Martijn J. Wilmer *

Department of Pharmacology and Toxicology, Radboud Institute for Molecular Life Science, Radboud University Medical Center, Nijmegen, The Netherlands

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ABSTRACT

The renal proximal tubule epithelium is responsible for active secretion of endogenous and exogenous waste products from the body and simultaneous reabsorption of vital compounds from the glomerular filtrate. The complexity of this transport machinery makes investigation of processes such as tubular drug secretion a continuous challenge for researchers. Currently available renal cell culture models often lack sufficient physiological relevance and reliability. Introducing complex biological culture systems in a 3D microfluidic design improves the physiological relevance of *in vitro* renal proximal tubule epithelium models. Organ-on-a-chip technology provides a promising alternative, as it allows the reconstruction of a renal tubule structure. These microfluidic systems mimic the *in vivo* microenvironment including multi-compartmentalization and exposure to fluid shear stress. Increasing data supports that fluid shear stress impacts the phenotype and functionality of proximal tubule cultures, for which we provide an extensive background. In this review, we discuss recent developments of kidney-on-a-chip platforms with current and future applications. The improved proximal tubule functionality using 3D microfluidic systems is placed in perspective of investigating cellular signalling that can elucidate mechanistic aberrations involved in drug-induced kidney toxicity.

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1. Introduction

The main physiological role of the kidneys is to clear endogenous waste products from the body. Exogenous drugs and toxins are often cleared via the same elimination route, making the kidney susceptible to drug-induced aberrations. Active cellular uptake of xenobiotics and metabolites by basolateral transport proteins contribute to the nephrotoxic potential of drugs (Cummings and Schnellmann, 2001). Renal sensitivity to drug-induced toxicity is further stimulated by the high fraction of cardiac output directed to the kidneys. This fraction is the driving force for renal filtration and tubular flow, resulting in high renal exposure to potential toxins. (Cummings and Schnellmann, 2001; Richards, 2008).

Early detection of adverse renal effects caused by lead compounds during drug development is seriously hampered by low predictive value of classical 2D cell culture models: compound attrition due to nephrotoxicity is only 2% in preclinical studies and rises to 9% in expensive clinical trials (Redfern et al., 2010). Recent studies support that reconstruction of the physiological microenvironment increases the clinical relevance of renal *in vitro* models and can lead to enhanced *in vitro* predictivity of drug-induced renal adverse effects.

A kidney-on-a-chip is a microfluidic device that allows culturing of living renal cells in 3D channels. Microfluidic technology is able to mimic a complicated 3D kidney structure allowing tubule growth, enable compartmentalization, offer constant flow resulting in fluid shear stress, and can include many different cell types (Wilmer et al., 2016). By recreating the renal tubule microenvironment, *in vitro* cellular responses are likely to approach the *in vivo* situation better compared to 2D systems. This would improve drug-induced toxicity screening and provide a promising tool to study 3D kidney regeneration.

This review will focus on current developments and future perspectives of proximal tubule kidney-on-a-chip techniques, with an emphasis on pharmacological interactions, drug-induced nephrotoxicity and tubular regeneration. To this end, the function of proximal tubule cells and its relation to fluidic shear stress is discussed. Finally, the development of multi-organ-chips and possible applications for regenerative medicine will be highlighted.

2. Functionality of the proximal tubule epithelium

Reconstruction of a proximal tubule in a physiological relevant environment will substantially contribute to our understanding of

* Corresponding author.
E-mail address: martijn.wilmer@radboudumc.nl (M.J. Wilmer).

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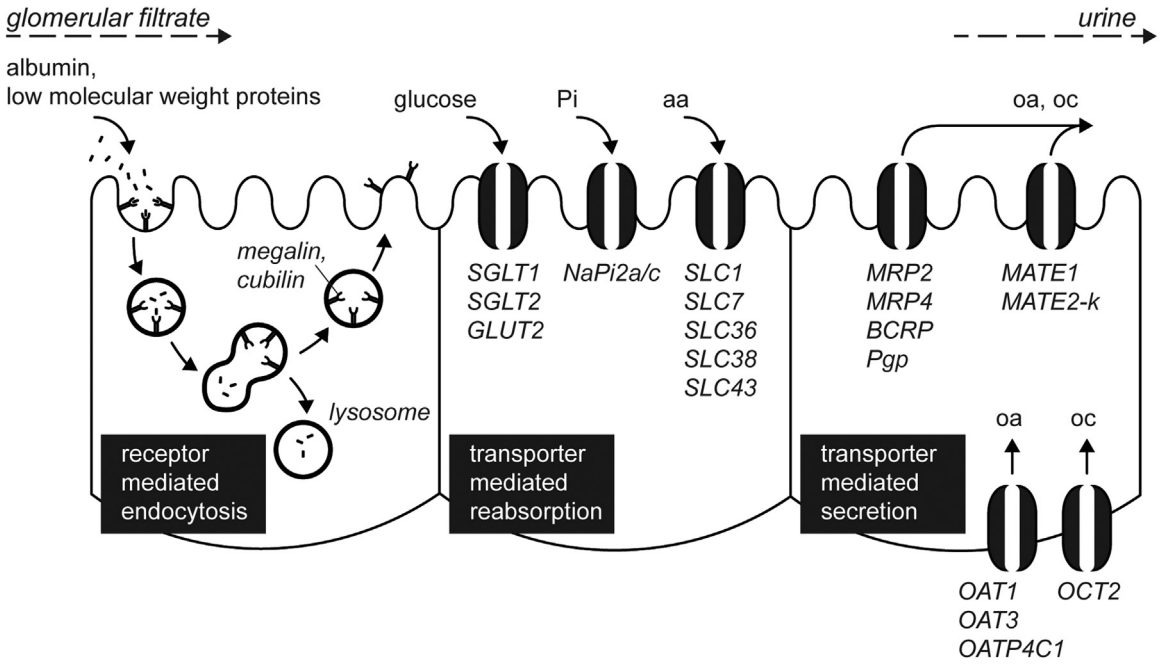

Fig. 1. Reabsorption and secretion by renal proximal tubule epithelial cells. Megalin and cubilin mediate endocytosis of low molecular weight proteins from the luminal side of the tubule. Apical transport proteins (SGLT, GLUT, NaPi, and SLC) mediate reabsorption of essential serum components, such as glucose, inorganic phosphate (Pi) and amino acids (aa) from the glomerular filtrate. Transcellular transport of organic anions (oa) and organic cations (oc) requires transporter mediated influx at the basolateral membrane and transporter mediated efflux at the apical membrane, acting in concert to facilitate selective renal elimination of waste compounds or drugs.

renal physiology and pharmacology. To evaluate the quality of a cultured system in terms of functional characteristics, a clear understanding of the relevant transport mechanisms in the proximal tubular epithelium is required (Fig. 1).

2.1. Receptor mediated endocytosis

Connected to Bowman's capsule, the proximal tubular lumen is exposed to the glomerular filtrate. The apical membrane of the proximal tubule forms a brush border and is extremely effective in the reabsorption of vital compounds that are freely filtered over the glomerular basement membrane. Low molecular weight proteins are largely reabsorbed from the glomerular filtrate via receptor mediated endocytosis. At the apical membrane, multi-ligand receptors megalin and cubilin bind low-molecular weight proteins in the glomerular filtrate with high capacity, which is followed by reabsorption via endocytosis (Nielsen et al., 2016). Low molecular weight proteinuria can consequently result from defects in this endocytic recycling machinery, for example caused by mutations in genes encoding transport proteins that are expressed at the lysosomal membranes. In the lysosomes, acidification results in dissociation of the receptor-ligand complex. Defects in receptor mediated endocytosis were reported for lysosomal transporter proteins chloride channel (CLC)-5 and cystinosin, which are associated with Dent's disease and nephropathic cystinosis, respectively (Wilmer et al., 2010a; Gorvin et al., 2013). A kidney-on-a-chip platform with an apical fluid flow and intact endocytic machinery will be valuable in future research of such pathological conditions, moreover as endocytosis under flow conditions was demonstrated to be increased (Ferrell et al., 2012; Jang et al., 2013; Raghavan et al., 2014).

Researchers often employed Opossum Kidney (OK) or Brown Norway rat yolk sac (BN-16) epithelial cells to study receptor mediated endocytosis, as these are known for their active megalin mediated endocytic machinery (Vegt et al., 2008; Lima et al., 2010; Ferrell et al., 2012). Although expression of megalin and the endocytic capacity is relatively high in these animal derived cells, the use of a human renal epithelial cell line will be the preferred model for pathological and pharmacological studies. For example, the human kidney cell line (HKC)-8 cell line was used to demonstrate that albumin-induced apoptosis targets the mitochondria (Erkan et al., 2007) and endocytosis of albumin in HKC-8 could be stimulated by phosphorylation of endocytic adaptor disabled-2 (Dab2) via protein kinase B (Akt) (Koral et al., 2014). Albumin reabsorption was also increased in primary human kidney proximal tubule epithelial cells exposed to laminar apical flow in a microfluidic device, pointing towards the influence of a physiological environment on proximal tubular function (Jang et al., 2013). A drawback of primary cells is the limited availability and batch-to-batch variations. The use of urine-derived proximal tubule epithelial cells allowed studying albumin uptake in cells isolated from patients with Dent's disease or nephropathic cystinosis that manifest with albuminuria. To obtain sufficient material, urine derived cells from healthy subjects and patients with mutations in the *CTNS* or *CLC5* genes were conditionally immortalized using SV40 temperature sensitive large T antigen (SV40T) and human telomerase reverse transcriptase (hTERT) (Wilmer et al., 2010b, 2011; Gorvin et al., 2013). These conditionally immortalized proximal tubule epithelial cells (ciPTEC) were used to demonstrate intact megalin dependent albumin and RAP reabsorption (Wilmer et al., 2010b; Caetano-Pinto et al., 2016), while defects in albumin reabsorption via megalin and cubilin mediated endocytosis were demonstrated in ciPTEC derived from patients with Dent's disease and nephropathic cystinosis (Gorvin et al., 2013; Ivanova et al., 2015). Together, studies using HKC-8 or ciPTEC can elucidate albumin handling in renal disease states such as acquired or inherited proteinuria. In respect of this review, the demonstration of fluidic shear stress affecting apical albumin handling in the proximal tubule epithelium supports that microfluidic devices should be used for future research focusing on receptor mediated endocytosis. Apical exposure to high levels of albumin under flow conditions can mimic albuminuria and microfluidic devices allow detailed (metabolic) analysis of the perfusion medium. In addition, urine-derived ciPTEC isolated from genetically well-characterized

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