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REVIEW ARTICLE

Kidney-based in vitro models for drug-induced toxicity testing

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Abstract

The kidney is frequently involved in adverse effects caused by exposure to foreign compounds, including drugs. An early prediction of those effects is crucial for allowing novel, safe drugs entering the market. Yet, in current pharmacotherapy, drug-induced nephrotoxicity accounts for up to 25% of the reported serious adverse effects, of which one-third is attributed to antimicrobials use. Adverse drug effects can be due to direct toxicity, for instance as a result of kidney-specific determinants, or indirectly by, e.g., vascular effects or crystals deposition. Currently used in vitro assays do not adequately predict in vivo observed effects, predominantly due to an inadequate preservation of the organs' microenvironment in the models applied. The kidney is highly complex, composed of a filter unit and a tubular segment, together containing over 20 different cell types. The tubular epithelium is highly polarized, and the maintenance of this polarity is critical for optimal functioning and response to environmental signals. Cell polarity is dependent on communication between cells, which includes paracrine and autocrine signals, as well as biomechanic and chemotactic processes. These processes all influence kidney cell proliferation, migration, and differentiation. For drug disposition studies, this microenvironment is essential for prediction of toxic responses. This review provides an overview of drug-induced injuries to the kidney, details on relevant and translational biomarkers, and advances in 3D cultures of human renal cells, including organoids and kidney-on-a-chip platforms.

Keywords Nephrotoxicity · Drug-induced kidney injury · In vitro models · Biomarkers

Abbreviations

L-DOPA	3,4-Dihydroxyl-L-phenylalanine
ADME	Absorption, distribution, metabolism, and excretion
AIN	Acute interstitial nephritis
AKI	Acute kidney injury
ATN	Acute tubular necrosis
ASC	Adult stem cell
ALP	Alkaline phosphatase
ARB	Angiotensin receptor blocker
ACEI	Angiotensin-converting enzyme inhibitors
ABC	ATP-binding cassette
ADPKD	Autosomal dominant polycystic kidney disease
B2 M	Beta-2 microglobulin
BUN	Blood urea nitrogen
BCRP	Breast cancer resistance protein
CRS	Cardiorenal syndrome
CKD	Chronic kidney disease
CLU	Clusterin
CIHP	Conditionally immortalized human podocyte
ciPTEC	Conditionally immortalized proximal tubule epithelial cell
CysC	Cystatin C
CYP	Cytochrome P450
ESKD	End-stage kidney disease
EMA	European Medicines Agency
ECM	Extracellular matrix
FDA	Food and Drug Administration
GGT	γ-Glutamyl transpeptidase
Gγ-GT	γ-Glutamyl transpeptidase transferase
GFR	Glomerular filtration rate
GMEC	Glomerular microvascular endothelial cell
GST	Glutathione S-transferase
HO	Heme oxygenase
HUS	Hemolytic-uremic syndrome
HRS	Hepatorenal syndrome

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HFM	Hollow fiber membrane
hTERT	Human telomerase reverse transcriptase
IVIVE	In vitro-to-in vivo extrapolation
iPSC	Induced pluripotent stem cell
IGFBP	Insulin-like growth factor-binding protein
IVIG	Intravenous immunoglobulin
IRI	Ischemia–reperfusion injury
KIM	Kidney injury molecule
L-FABP	Liver type-fatty acid binding protein
MMP	Matrix metalloproteinase
MTX	Methotrexate
MEM	Microelectromechanical systems
MPS	Microphysiological systems
MCP	Monocyte chemotactic protein
MATE	Multidrug and toxin extrusion protein
MRP	Multidrug resistance protein
NAG	*N*-Acetyl-β-glucosaminidase
NGAL	Neutrophil gelatinase-associated lipocalin
NSAIDs	Nonsteroidal anti-inflammatory drugs
OAT	Organic anion transporters
OCT	Organic cation transporter
OPN	Osteopontin
P-gp	P-glycoprotein
PBPK	Physiologically based pharmacokinetic
PES	Polyethersulfone
PSTC	Predictive Safety Testing Consortium
RPA	Renal papillary antigen
RPTEC	Renal proximal tubule epithelial cell
RAS	Renin-angiotensin system
RBP	Retinol binding protein
sCr	Serum creatinine
SV40T	Simian virus 40 large T antigen
SDS	Sodium dodecyl sulfate
SLC	Solute carrier family
3D	Three-dimensional
TIMP	Tissue inhibitor of metalloproteinase
TEER	Transepithelial electrical resistance
TFF	Trefoil factor
2D	Two-dimensional
uALB	Urinary albumin
uTP	Urinary total protein

Introduction

The kidneys play an essential role in preserving homeostasis of the body's internal environment, including regulation of water, electrolyte, nitrogen, and acid–base balances. They also control the red blood cell production and blood pressure (Bello-Reuss and Reuss 1983). Impaired renal function is commonly observed in clinical practice and is often associated with the use of drugs. One-third of all drugs and drug candidates are excreted unchanged from the body by the kidneys, and drug-induced nephrotoxicity accounts for 20% of all episodes that lead to acute kidney failure (Naughton 2008b).

Human kidneys contain around 1 million nephrons. A nephron is composed of different subunits and includes the glomerulus, proximal tubule, loop of Henle, distal tubule, and the collecting duct (Lote 2012) (Fig. 1). All subunits contribute to the excretory function of the kidney in three steps: glomerular filtration, tubular reabsorption, and tubular secretion (Koeppen and Stanton 2013). During glomerular filtration (Fig. 2), blood plasma is filtered in the glomerulus, a bundle of porous capillaries lined by a membrane and specialized epithelial cells, that allows solutes and waste, including drugs and their metabolites, and water to pass through while ensuring larger substances, such as blood cells and proteins, remain in the circulatory system (Holechek 2003). Protein-bound molecules, including drugs, are eliminated by proximal tubular secretion via a well-coordinated process of uptake by the tubular cells at the blood-facing basolateral site and secretion into the tubular lumen. Tubular reabsorption begins as soon as the filtrate enters the lumen of the proximal tubule, and involves the reabsorption of organic nutrients, such as glucose, and hormonal-regulated reabsorption of ions coupled with passive water reabsorption. Megalin and cubilin receptors at the apical membrane are responsible for endocytosis-mediated reuptake of filtered low-molecular-weight proteins, such as β2-microglobulin (Eshbach and Weisz 2017). As the filtrate travels along the nephron, some drugs, hydrogen ions, and ammonia are secreted into the collecting tubule (Feher 2017).

Even though the main function of the kidney is to excrete waste products from the bloodstream, it is important to mention that the kidney is also a major endocrine organ. Five very important hormones/enzymes are produced by the kidney, viz, 1,25-dihydroxyvitamin D3, erythropoietin, renin, Klotho, and kallikrein (Haussler et al. 2016); (Shimamoto and Iimura 1989). Calcitriol, 1,25-dihydroxyvitamin D3, is activated in the proximal tubule and acts in the reabsorption of calcium, but it is also involved in bone health and in the regulation of parathyroid function (Kumar et al. 2012). Erythropoietin is produced by peritubular capillary endothelial cells in the proximal tubule, and acts by stimulating the production of red blood cells in the bone marrow (Ohana et al. 2013). Renin is secreted by granular cells of the juxtaglomerular apparatus. This enzyme also known as angiotensinogenase is the key factor of the renin–angiotensin system (RAS) that leads to the production of the potent vasoconstrictor angiotensin controlling blood pressure (Lopez and Gomez 2010). Klotho is synthesized and secreted by the distal tubule. Similar to calcitriol, Klotho is involved in the calcium and phosphate homeostasis (Kim et al. 2015). Kallikrein of the renal kallikrein–kinin system is found in

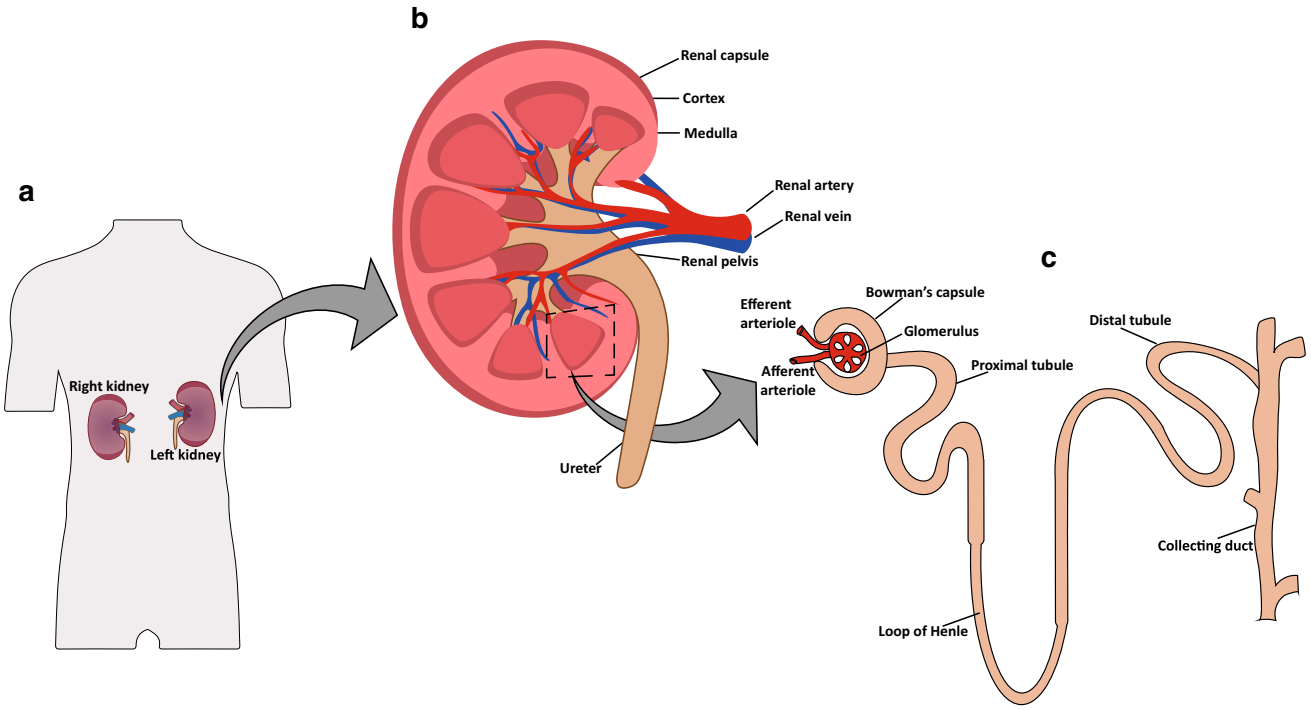


Fig. 1 Human kidney anatomy. External view (**a**), internal view (**b**), and its functional unit nephron (**c**)

the distal tubule, and is involved in the regulation of blood pressure (Kakoki and Smithies 2009).

Due to the complexity of the kidney, as an organ containing specialized structures and multiple cell types, it becomes quite difficult to find a reliable model system to study the effects or toxicity of drugs and their metabolites on this organ. In this review, detailed information on drug-induced kidney injury mechanisms and available in vitro models to predict this with relevant translational biomarkers will be discussed, with an emphasis on novel developments in the field of microphysiological systems that meet the requirements of the 3Rs (replacement, reduction, refinement) of animal experiments for drug safety screenings.

Drug-induced kidney injury

Exposure to various drugs or drug candidates for therapeutic or diagnostic purposes (Fig. 3) could possibly lead to toxicity in the kidney, resulting in damage of the tubules, interstitium, glomerulus, or renal microvasculature, and consequently resulting in various clinical manifestations (Table 1) (Małyszko et al. 2016). About 36% of nephrotoxicity incidence has been attributed to antimicrobials (e.g., aminoglycosides). While in most cases, the drug-induced kidney injury is reversible upon cease of treatment some medications could lead to chronic dysfunction such as papillary necrosis, tubulointerstitial nephritis, or prolonged proteinuria (Choudhury and Ahmed 2006). Nephrotoxicity of most drugs is more severe in patients already suffering from kidney disease (Vervaet et al. 2017).

Kidneys can experience both structural damage and loss of function

Acute kidney injury (AKI) is characterized by an increase in blood levels of waste solutes, such as urea and creatinine, and often oliguria and electrolyte disorders. AKI can be classified into three categories: prerenal, intrinsic, and postrenal (Makris and Spanou 2016). In prerenal AKI, the kidney may function normally, but there is a decrease in either intravascular volume or arterial pressure, which results in a reduced glomerular filtration rate (GFR) (Macedo and Mehta 2009). RAS inhibitors such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers can also lead to prerenal AKI, as it causes dilation of the efferent arteriole which contributes to reduced intraglomerular pressure (Navis et al. 1996). Furthermore, nonsteroidal anti-inflammatory drugs (NSAIDs) are known to decrease the GFR by changing the balance of vasodilatory/vasoconstrictive agents in the renal microcirculation (Dixit et al. 2010). The most common type of intrinsic AKI is acute tubular necrosis, which is usually caused by ischemia or toxic injury (Basile et al. 2012). Postrenal AKI occurs when there is an obstruction of urinary flow that can lead to impaired renal blood

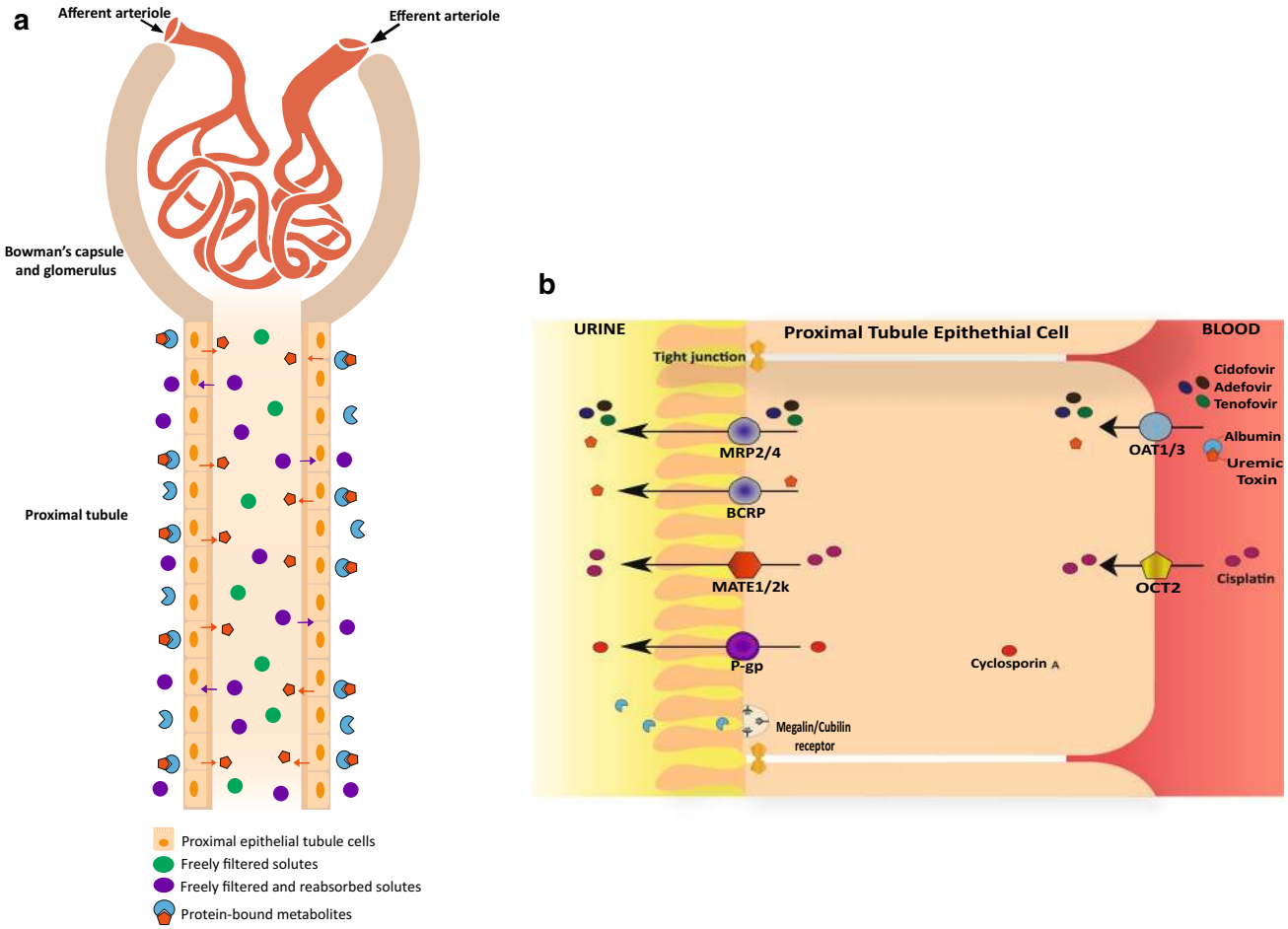


Fig. 2 The renal proximal tubule. **a** Blood plasma solutes and proteins pass through the glomerular filter. Organic and inorganic solutes (in green) are freely filtered by the glomerulus. Some solutes, such as glucose and amino acids (in purple), are reabsorbed completely by the proximal tubule epithelial cells and transferred back to the systemic circulation. Protein-bound metabolites (in orange) are actively secreted by the proximal tubule epithelial cells. **b** Drug transporters involved in nephrotoxicity. The organic anion transporters OAT1 (*SLC22A6*) and OAT3 (*SLC22A8*) are involved in the uptake of known antiviral agents, such as cidofovir, adefovir, and tenofovir, which will then be secreted by MRP2 (*ABCC2*) and MRP4 (*ABCC4*) located at the apical side of the membrane. The chemotherapeutic agent cisplatin is imported by OCT2 (*SLC22A2*) and exported via MATE1 (*SLC47A1*) and MATE2-k (*SLC47A2*). P-gp (*ABCB1*) is involved in the secretion of the immunosuppressant cyclosporin A. Uremic toxins, such as Indoxyl sulfate and kynurenic acid, are uptaken via OAT1 and excreted by MRP2/4 and BCRP (*ABCG2*) (color figure online)

flow and inflammatory processes, seen for example in urate and oxalate imbalances (Makris and Spanou 2016).

When these changes become persistent both in structure and function, AKI may progress to chronic kidney disease (CKD), and when not properly treated, it can lead to end-stage kidney disease. The GFR is used to categorize CKD in five distinct stages, along with the presence or absence of proteinuria (Kipp and Kellerman 2009).

Nephrotoxicants, including chemotherapeutics, drugs of abuse, antimicrobials, radiocontrast agents, environmental pollutants, and natural substances, can induce kidney injury via similar mechanisms. Renal cell death can be mediated by drug transporters that determine the selectivity for the tubular cell, mitochondrial damage, and drug metabolism (Barnett and Cummings 2018). The reabsorption of solutes by the kidneys is a task that demands a large consumption of energy. The proximal tubule is the nephron's segment that is the most susceptible to toxic effects due to its role in absorption and secretion, both requiring high rates of oxidative metabolism. For this reason, mitochondrial damage will lead to a reduction in ATP production that in turn will increase oxidative stress, disrupt cell volume, ion concentrations, and apoptosis or, in severe cases necrosis, thus compromising renal function (Eirin et al. 2017). Renal transporters may facilitate drugs to enter the tubular cells, sometimes followed by metabolism leading to their bioactivation (Liang et al. 2015a). These transporters belong to two large families: the solute carrier family (SLC) and the

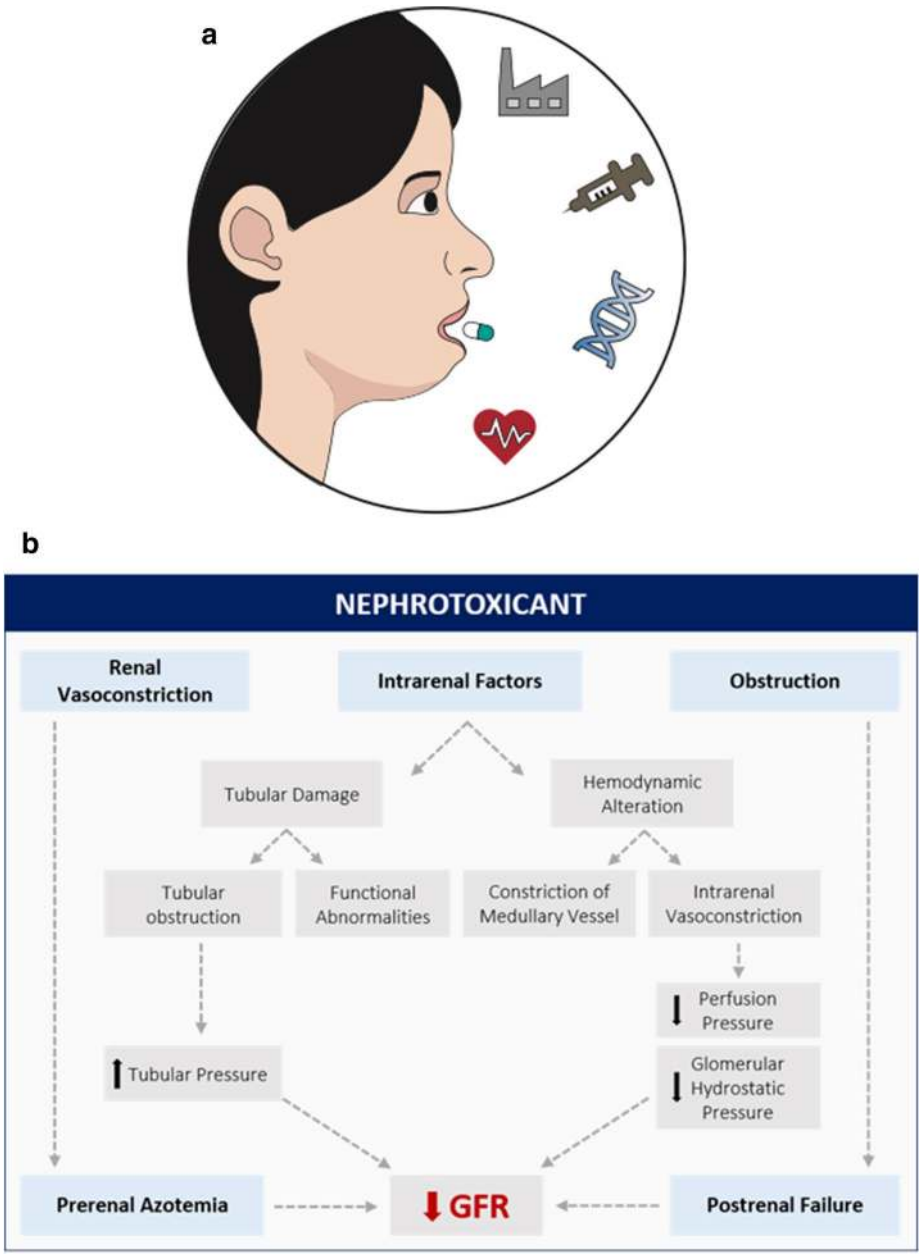


Fig. 3 Risk of drugs to affect kidney function. **a** The human body is subjected to a variety of nephrotoxicants, including chemotherapeutics, drugs of abuse, antimicrobials, environmental pollutants, and natural substances, which can induce kidney injury via several mechanisms. **b** These nephrotoxicants can lead to acute kidney injury (AKI). AKI is characterized by gradual loss of kidney function that, when not properly treated, can lead to irreversible kidney failure. Renal vasoconstriction, intrarenal factors, and obstruction are some of the effects of the nephrotoxicants on the kidney, which will lead to a decrease in the glomerular filtration rate (GFR). An estimation of the GFR is widely used in clinic as an indicator of kidney function

adenosine triphosphate (ATP)-binding cassette (ABC) transporter family. Uptake of organic anions (Fig. 2) is mediated by the organic anion transporters 1 (OAT1; *SLC22A6*) and 3 (OAT3; *SLC22A8*) and their removal from the cell via breast cancer resistance protein (BCRP; *ABCG2*), multidrug resistance protein 2 (MRP2; *ABCC2*) and 4 (MRP4; *ABCC4*) (Giacomini et al. 2010; Nigam 2018; Nigam et al. 2015). Organic cations (Fig. 2) are transported into tubular cells predominantly via the basolateral organic cation transporter 2 (OCT2; *SLC22A2*) and then excreted into the tubular lumen via multidrug and toxin extrusion protein 1 (MATE1; *SLC47A1*) and 2-k (MATE2-k; *SLC47A2*) and P-glycoprotein (P-gp; *ABCB1*). Although most drugs are metabolized by the liver, some nephrotoxicants are known to be dependent on kidney metabolism as this organ also expresses Phase I (CYPs) and Phase II (GSTs) enzymes (Anders 1980).

Vascular injury

Several immunosuppressive agents such as cyclosporin, tacrolimus, and muromonab-CD3 may cause renal vascular injury by damaging primary endothelium that induces platelet aggregation and consumption. Such an effect is also associated with antiplatelet agents, for instance, ticlopidine and clopidogrel, and chemotherapeutic agents (e.g., mitomycin

Table 1 Commonly used nephrotoxic drugs and associated toxicities

Therapeutic class	Drugs	Toxic events	References
Anticoagulants	Warfarin, heparin	Renal tissue ischemia Necrosis Infarction	Brodsky (2014)
Anticonvulsant	Phenytoin	Acute interstitial Nephritis Diabetes insipidus	Ghane Shahrbaf and Assadi (2015)
Antidepressant	Amitriptyline	Rhabdomyolysis	Coco and Klasner (2004)
	Lithium	Chronic interstitial Nephritis Glomerulonephritis Rhabdomyolysis	Azab et al. (2015) and Coco and Klasner (2004)
Antifungal agent	Amphotericin B	ATN Renal tubular acidosis (RTA) Electrolyte imbalance Urinary concentration Defects	Deray (2002)
Antihistamine	Diphenhydramine, doxylamine	Rhabdomyolysis	Coco and Klasner (2004)
Antihypertensive	Hydralazine, minoxidil	Prerenal azotemia	Ejaz et al. (2004)
	Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers	Renal artery stenosis Volume depletion	Palmer (2002)
Antimicrobials	Aminoglycosides	Hypomagnesemia nonoliguric ATN Chronic tubulointerstitial nephritis Fanconi syndrome	Lopez-Novoa et al. (2011)
	Vancomycin	Acute tubular necrosis Tubular damage	Htike et al. (2012) and Liu et al. (2015)
	Ciprofloxacin	AIN Crystalluria	Bird et al. (2013)
	Penicillin	Glomerulonephritis	Naughton (2008a)
	Cephalosporin	Acute interstitial nephritis	Naughton (2008a)
Antiplatelet	Ticlopidine, clopidogrel and quinine	Thrombotic microangiopathy Renal vascular injury	Medina et al. (2001)
Antiretroviral agents	Cidofovir, adefovir	Proximal tubule damage	Kalyesubula and Perazella (2011)
	Tenofovir	ATN Proximal tubulopathy	Fernandez–Fernandez et al. (2011) and Jafari et al. (2014)
	Indinavir	Tubular crystallization Nephrolithiasis	Kalyesubula and Perazella (2011)
	Atazanavir	AIN	Hara et al. (2015)
Antiviral	Valaciclovir	Thrombotic microangiopathy Renal vascular injury	Izzedine et al. (2005)
	Acyclovir	Tubular crystallization	Yildiz et al. (2013)
	Foscarnet	Crystal deposition Electrolyte abnormalities	Frochot et al. (2016)
Bisphosphonates	Bisphosphonate zoledronate	Deranged Na–K-ATPase Loss of brush border Apoptosis	Markowitz et al. (2003)
Calcineurin inhibitor	Rapamycin	Tubular collapse Vacuolization Nephrocalcinosis	Marti and Frey (2005)

Table 1 (continued)

Therapeutic class	Drugs	Toxic events	References
Chemotherapeutic agent	Cisplatin	Proximal tubular necrosis Tubular cell deletion	Miller et al. (2010)
	Nedaplatin	Lysosomal hyperplasia Necrosis and hyperplasia of renal papilla and collecting duct	Uehara et al. (2011)
	Mitomycin C	Thrombotic microangiopathy Renal vascular injury	Lameire (2014)
	Ifosfamide	Proximal tubular Dysfunction Fanconi-like syndrome	Nissim et al. (2006)
	Methotrexate (MTX)	Tubular crystallization ATN	Widemann and Adamson (2006)
	Pemetrexed	ATN Nephrogenic diabetes insipidus (NDI) RTA	Zajjari et al. (2017)
Contraceptive	Estrogen containing	Hemolytic uremic syndrome	Choudhury and Ahmed (2006)
Diuretics	Thiazides, loop, potassium-sparing	Prerenal azotemia	Naughton (2008a)
Immunomodulatory	Intravenous immunoglobulin (IVIG)	Osmotic nephrosis	Levy and Pusey (2000)
Immunosuppressive	Cyclosporin	Decreased glomerulus filtration rate	Busauschina et al. (2004)
	Cyclosporin, tacrolimus and muromonab-CD3	Thrombotic microangiopathy Renal vascular injury	Olyaei et al. (2001)
Narcotic analgesic	Cocaine, heroin, methadone	Rhabdomyolysis	Alinejad et al. (2016) and McCann et al. (2002)
Non-narcotic analgesic	Aspirin, acetaminophen	Chronic interstitial nephritis	Sampathkumar et al. (2016)
	Nonsteroidal anti-inflammatory drugs	Glomerulonephritis Acute interstitial nephritis Chronic interstitial nephritis Prerenal azotemia Acute papillary necrosis Membranous nephropathy	Lucas et al. (2019) and Naughton (2008a)
Osmotic agents	Mannitol, dextran	Isometric vacuolization Swelling of proximal tubule	Choudhury and Ahmed (2006)
Thrombolytic agents	Streptokinase and tissue-plasminogen activator	Renal tissue ischemia Necrosis Infarction	Eddy and Fogo (2006)

C and gemcitabine; Table 1) (Choudhury and Ahmed 2006). The narrow arteries of the kidney including glomerular capillaries, and interlobular and arcuate arteries can be clogged by arterial cholesterol plaques following administration of thrombolytic agents (e.g., streptokinase) and anticoagulants (e.g., warfarin). This can result in ischemia, infarction, necrosis, and inflammation of the surrounding interstitium, often also affecting tubular cells leading to acute tubular necrosis (ATN; Table 1) (Hitti and Anderson 2005).

Tubular injury

Proximal tubule cells absorb and concentrate compounds from the glomerular filtrate as well as from the systemic circulation, and are prone to be affected by nephrotoxic drugs. These drugs can cause tubular toxicity by various mechanisms such as oxidative stress, diminishing mitochondrial function, restricting tubular transport processes, and generating oxidative stress (Perazella 2005). Drugs such as antimicrobials, chemotherapeutics, radiocontrast agents, immunosuppressives, and bisphosphonates are associated with tubular injury. These xenobiotics disrupt tubular cell polarity which, along with the expression of apical and basolateral transporters, is crucial for tubular cell function. This leads to the dislocation of apical and basolateral transporters (e.g., Na/K-ATPase) resulting in a leaky epithelium. Furthermore, subsequent increase in intracellular calcium disrupts ion homeostasis, leading to cell death (Lameire et al. 2005).

Inflammation

Induction of inflammatory responses in the glomerulus, renal tubular cells, and the surrounding interstitium is another mechanism of drug-induced nephrotoxicity that can lead to fibrosis and renal scarring (Naughton 2008b). An immune-mediated inflammatory condition, glomerulonephritis, has been reported to be induced by several medications such as penicillin and NSAIDs (Table 1) and is associated with proteinuria (Frazier and Obert 2018). Inflammation can also be a complication of lithium, although less well known than its tubulotoxic effects. Another inflammatory condition, acute interstitial nephritis (AIN), occurs as adverse reaction to several drugs that are assumed to induce an immune response by binding to the antigens in the kidney. Medications such as antimicrobials, phenytoin, proton-pump inhibitors, allopurinol, lithium, and antivirals have been implicated in this condition (Rossert 2001).

Crystal nephropathy

Various drugs and their derivatives may lead to precipitation of crystals within the distal tubular lumen because of their insolubility in urine, thereby restricting urine flow and triggering a cellular reaction in the interstitium. Renal insufficiency and intravascular volume depletion increase the risk of crystal nephropathy. Concentration of the drug in the urine and urinary pH may influence the precipitation of crystals and volume repletion and adjustment of urinary pH, improving solubility, may be of benefit. Medications associated with crystal nephropathy include antivirals and antimicrobials as mentioned in Table 1 (Markowitz and Perazella 2005).

Patient-specific risk factors

Some patients are more susceptible to develop drug-induced nephrotoxicity. Volume depletion increases the risk by changing the drug concentration to a toxic level. Hypoalbuminemia, commonly observed in cirrhotic patients, increases the risk of unwanted drug overdose by elevating the serum concentration of the unbound drug fractions (Pazhayattil and Shirali 2014). Both elderly and neonates possess a particular risk for drug-induced nephrotoxicity. Comorbid conditions and administration of multiple nephrotoxic drugs carry a significant burden to elderly patients, while premature delivery predisposes neonates to develop kidney function impairment (Patzer 2008). In addition, individual genetic makeup, responsible for variable metabolic pathways and related drug sensitivity, can also influence the vulnerability of kidneys to nephrotoxicants. Polymorphisms in genes encoding enzymes that are involved in drugs' metabolism and elimination processes may increase the risk of nephrotoxicity. For instance, polymorphism of cytosolic glutathione-S-transferase (GST) enzyme elevates the risk for cisplatin-induced nephrotoxicity, since this enzyme can, to a certain extent, detoxify reactive molecules (Petros et al. 2005). A systematic review on inter-individual differences in cisplatin-induced nephrotoxicity has recently pointed towards three genes (*SLC22A2*, and two DNA repair genes) that determine sensitivity, suggesting that patient-specific dose optimization can be applied according to the genetic makeup. This approach could possibly reduce cisplatin toxicity (Zazuli et al. 2019).

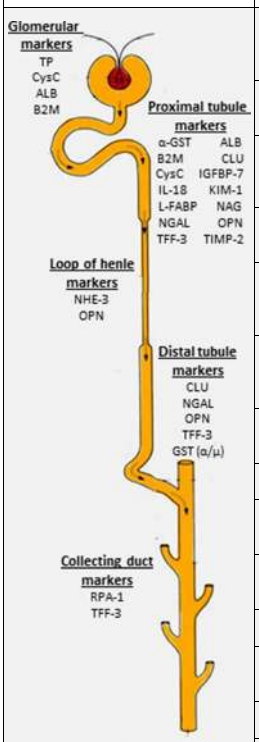
Kidney failure due to remote organ damage

Several risk factors such as genetics, obesity, diabetes, cardiovascular disease, and age can increase the chances of an individual to develop kidney disease, or when already diagnosed, it can gradually drive the progression of the disease (Kazancioğlu 2013). It is important to note that renal dysfunction can also be affected by the performance of distinct organs, such as the heart, lung, and liver. As the kidneys receive ~25% of the cardiac output, a condition known as cardiorenal syndrome (CRS) can manifest when either the heart or the kidneys fail (Ronco et al. 2012). Considering that some segments of the nephron are highly sensitive to oxygen variations, if the lung is injured it can cause severe hypoxemia which in time can reduce renal blood flow, contributing to renal impairment as well (Basu and Wheeler 2013). Patients suffering from cirrhosis can develop hepatorenal syndrome (HRS), which can lead to damage and degeneration of the kidney. If the hepatic metabolism is compromised, a downregulation of cytochrome P450 (CYP) enzymes activity can lead to an accumulation of nephrotoxic drugs in the systemic circulation, resulting in kidney injury (Lane et al. 2013).

Biomarkers for drug-induced kidney injury

Creatinine and urea have long been considered as the "gold standard" to identify drug-induced nephrotoxicity and to detect renal dysfunction. However, various limitations of these two biomarkers, including low sensitivity and specificity, delayed rise in plasma because of functional reserve, and extrarenal clearance, demand for novel renal biomarkers to early detect and monitor drug-induced nephrotoxicity with high specificity and sensitivity. To address this, new potential markers are continuously being developed and qualified, resulting in a substantial increase of biomarker research (Xie et al. 2013). Until now, several biomarkers have been identified, as enlisted in Table 2. A biomarker qualification data submission released by the Predictive Safety Testing Consortium (PSTC) in 2009 included urinary kidney injury molecule-1 (KIM-1), urinary trefoil factor 3 (TFF-3), urinary beta-2 microglobulin (B2 M), urinary cystatin C (CysC),

Table 2 Overview of renal toxicity biomarkers

Picture	Biomarker	Species	Indicator	Limitation	Biomarker type	References
	Kidney injury molecule-1 (KIM-1)	Humans, rats and mice	Proximal tubular damage	Not suitable as early marker and not specific	Injury	Vaidya et al. (2008a, b) and Vlasakova et al. (2014)
	Trefoil factor 3 (TFF3)	Humans and rats	Proximal tubular dysfunction		Functional	(Chapman et al. 2015; Xiao et al. 2014)
	N-acetyl-β-D-glucosamininidase (NAG)	Humans and rats	Proximal tubular damage	Inhibited by endogenous urea, no specificity	Leakage and functional	(Vaidya et al. 2008a; Vlasakova et al. 2014)
	α-Glutathione S-Transferase (α-GST)	Humans and rats	Proximal tubular damage		Leakage	(Walshe et al. 2009; Wang et al. 2018)
	γ-Glutamyl Transferase (GGT)	Humans and rats	Proximal tubular damage			Andreucci et al. (2017) and Vaidya et al. (2008a)
	alkaline phosphatase (ALP)	Humans and rats	Proximal tubular damage			Andreucci et al. (2017) and Chapman et al. (2015)
	Clusterin (CLU)	Humans, rats and dogs	Proximal tubular damage	Clinical data is not extensively available	Injury	Wu et al. (2018)
	IL-18	Humans and mice	Proximal tubular damage	Not specific and lower sensitivity	Injury	Pazhayattil and Shirali (2014)
	Insulin-like Growth factor-Binding Protein 7 (IGFBP-7)	Humans	Proximal tubular damage	Less accuracy	Injury	Jia et al. (2017)
	Tissue Inhibitor of Metalloproteinases-2 (TIMP-2)	Humans	Proximal tubular damage	Less accuracy	Injury	Jia et al. (2017)
	Heme oxygenase-1 (HO-1)	Humans and mice	Proximal tubular damage		Injury	Weber et al. (2017)
	Na^+/H^+ exchanger isoform 3 protein (NHE-3)	Humans	Proximal tubular damage		Injury	du Cheyron et al. (2003)
	Albumin (ALB or uALB)	Humans and rats	Proximal tubular and glomerular dysfunction		Functional	(Vlasakova et al. 2014)
	Retinol Binding Protein (RBP)	Humans	Proximal tubular and glomerular dysfunction	Less specificity and limited detection	Functional	Vlasakova et al. (2014)
	β2-Microglobulin (B2M)	Humans and rodants	Proximal tubular damage and glomerular damage	Less specificity and instability at acidic pH in urine	Functional	Chapman et al. (2015)
	Serum creatinine (SCr)	Humans and rats	Change in GFR	Poor sensitivity and specificity and poor accuracy	Functional	Andreucci et al. (2017)
	Matrix metalloproteinase 9 (MMP-9)	Humans	Glomerular injury	Less sensitive for case-control study	Injury	Han et al. (2008)
	Cysteine-rich 61 (Cyr61)	Humans	Glomerular injury	Disappear quickly in urine	Injury	Sawai et al. (2007)
	π-Glutathione S-Transferase (π-GST)	Humans and rats	Distal tubular damage			Andreucci et al. (2017)
	Urinary total protein (TP or uTP)	Humans and rats	Glomerular and tubular dysfunction		Functional	Vlasakova et al. (2014) and Xie et al. (2013)
	Serum cystatin C (serum Cys C)	Humans and rats	Change in GFR and tubular dysfunction	Unreliable marker of GFR when proteinuria is present	Functional	Ozer et al. (2010)
	NGAL (Neutrophil Gelatinase-Associated Lipocalin)	Humans, mice and rats	Proximal tubular damage and distal tubular damage	Affected by interference factors	Injury	Bolignano et al. (2008)
	Liver type- Fatty Acid Binding Protein (L-FABP)	Humans	Proximal tubular damage and distal tubular damage.	Not well established for contrast induced AKI	Functional	Kamijo et al. (2006) and Manabe et al. (2012)
	Renal papillary antigen-1 (RPA-1)	Rats	Papillary necrosis			Price et al. (2010)
	Osteoactivin	Humans and rodents	Tubular damage		Injury	Pahl et al. (2010)
	Osteopontin (OPN)	Humans and rats	Tubular damage		Injury	Xie et al. (2001)
	Midkine (MK)	Humans	Tubular damage			Hayashi et al. (2017)
	miRNA	Humans and rats	Vascular damage		Injury	Liu et al. (2019)
	Netrin-1	Humans and mice	Early renal damage		Functional	Reeves et al. (2008)
	Fetuin-A	Humans and mice	Autosomal dominant polycystic kidney disease (ADPKD)	Limited clinical application	Functional	Piazzon et al. (2015)
	Monocyte chemotactic protein 1 (MCP-1)	Humans	Ischemia–reperfusion injury (IRI), schistosomal nephropathy		Injury	Hanemann et al. (2013) and Liu et al.(2016)

urinary albumin (uALB), urinary total protein (uTP), and urinary clusterin (CLU) as emerging biomarkers to study xenobiotic-induced kidney injury in rat (Dieterle et al. 2010b). Later in 2014, with the support of Food and Drug Administration (FDA) and European Medicines Agency (EMA), the PSTC included neutrophil gelatinase-associated lipocalin (NGAL) and osteopontin (OPN) for further evaluation as emerging biomarkers (Dieterle et al. 2010b).

KIM-1, a sensitive and specific damage marker of proximal tubule epithelial cells, can cleave and move into the tubule lumens upon diverse primary and secondary renal damages. It is found up-regulated in CKD with renal fibrosis and is significantly elevated in early stages of AKI. It is considered an early marker for detection, progression, and outcome of kidney diseases. However, increased KIM-1 may also play role in renal tubular epithelial cells' regeneration after acute injury (Xie et al. 2013; Yin and Wang 2016). One of the least studied, biologically qualified urinary markers is TFF3, which is reduced significantly in a time- and dose-dependent manner following proximal tubular damage. This small peptide hormone is also found to correlate with the severity of kidney lesions and is considered as a sensitive marker for AKI (Yu et al. 2010). B2M is a low molecular-weight protein filtered completely and almost completely reabsorbed by the proximal tubule. Therefore, a significant increase of B2M is observed in urine following a minor impairment in tubular uptake. Thus, urine B2M is considered as a potential indicator of impaired function during drug-induced nephrotoxicity. In addition, glomerular injury can also elevate urinary excretion of B2M and it has, therefore, been qualified as glomerular injury marker as well in rodents (Dieterle et al. 2010a). Contrary to the conventional renal function biomarkers, CysC exhibits high sensitivity and specificity in monitoring acute and chronic renal impairments. Determination of CysC levels can be used to diagnose early stages of renal dysfunction and to monitor functional alterations over time. This biomarker is considered a better diagnostic tool for pre-clinical renal disease and is found to be a more accurate detector of early stage diabetic nephropathy (Onopiuk et al. 2015). Its plasma level is used as glomerular marker for GFR and the urine level as functional marker of proximal tubule, since it is a low-molecular-weight protein that needs to be reabsorbed by megalin. Urinary albumin (uALB) has been considered a well-established diagnostic and prognostic marker to study the extent of glomerular injury in CKD. Because of its specificity to intrinsic causes such as rhabdomyolysis and ischemic–reperfusion, it remains unchanged in prerenal and postrenal events of AKI (Bolisetty and Agarwal 2011).

Another early marker of renal damage is urinary clusterin (CLU), which is a heterodimeric glycoprotein that contributes to cellular interaction, lipid transport, and initiation of apoptosis during renal damage. Like KIM-1, expression of CLU is significantly elevated in dedifferentiated tubular cells during AKI but also in polycystic kidney disease, nephrectomy, and renal cell carcinoma (Hidaka et al. 2002). This marker has been found as a promising indicator of tubulointerstitial renal lesions and able to predict end-stage kidney disease (ESKD) (Wu et al. 2018), and also helps in triaging of patients with delayed graft function in less than 4 h after transplantation (Pianta et al. 2015). A lysosomal enzyme of proximal tubule, *N*-acetyl-β-glucosaminidase (NAG), is a persistent, sensitive, quantitative and robust biomarker of proximal tubular injury. It has been found elevated following kidney diseases such as AKI, diabetic nephropathy, and chronic glomerular diseases (Vaidya et al. 2008a). Some other enzymes, such as GST, γ-glutamyl-transferase (GGT), and alkaline phosphatase (ALP), released from proximal and distal tubule cells into urine relate to early damage. In AKIs, two subtypes of GST, α and π, are released from proximal and distal tubule, respectively, allowing to distinguish between the two segments when affected (Wang et al. 2018). As GGT and ALP increase during damage in the brush border, elevated levels of these enzymes were associated with complicated pyelonephritis and renal impairment (Han et al. 2019).

Models for nephrotoxicity screening

Conventional in vitro models

Until recently, researchers were left with only two options: in vitro cultures of primary human cells or the use of animal models, both having limitations. Primary cells are used as they mimic the physiological state of cells in vivo most closely; however, these cells have a limited growth capacity and tend to lose their phenotype over time (Table 3). Despite these limitations, primary renal cells still remain a reliable option to study basic renal cellular functions and the effects of nephrotoxicants thereon. To overcome the difficulty in culturing primary cells, immortalized cells can be used because of their capacity to grow and divide indefinitely. The disadvantages of these cells include the immortalization procedure that by itself may result in some changes that, over time, can alter the functions and characteristics of cells (Bajaj et al. 2018). Animal models are used as they can fill the gap that in vitro models often have, viz, the lack of physiological resemblance. However, the use of animal models is expensive, requires a lot of time and expertise, has low throughput potential, poses ethical issues, but most importantly, these models often do not correlate to human systems (Barré-Sinoussi and Montagutelli 2015).

Being the proximal tubule a major target for many nephrotoxicants, it is logical that cell-based in vitro models that seek to resemble this segment of the nephron should

be characterized by the expression of important markers, including *SLC22A6* (OAT1), *SLC22A8* (OAT3), *SLC22A2* (OCT2) on the basolateral membrane and *ABCB1* (P-gp), *SLC47A1* (MATE1), *SLC47A2* (MATE2), *ABCC2* (MRP2), *ABCC4* (MRP4), *ABCG2* (BCRP), and the endocytosis receptors megalin and cubilin on the apical membrane (Bajaj et al. 2018) (Fig. 2). Although often applied, the immortalized HK-2 cell line lacks the expression of OAT1, OAT3, OCT2, MRP2, and BCRP, and may be not a representative model to study nephrotoxicity (Jenkinson et al. 2012b).

Two important immortalized cell lines have been extensively used for nephrotoxicity screening: RPTEC/TERT1 and ciPTEC. The RPTEC/TERT1 cell line was immortalized using the human telomerase reverse transcriptase (hTERT) (Simon-Friedt et al. 2015), whereas ciPTEC lines obtained either from urine or kidney tissue were transfected using hTERT and a temperature-sensitive mutant of SV large T antigen (SV40T), allowing these cells to proliferate at 33 °C and mature at 37 °C (Jansen et al. 2014; Wilmer et al. 2010) (Table 3). These cell lines surpass HK-2 cells by expressing all relevant markers cited above; however, OAT function was only attained after lentiviral transduction (Nieskens et al. 2016). Using the same immortalization procedure in the ciPTEC line, a podocyte cell line (CIHP) was generated. As these cells maintain the filtration barrier of the glomeruli, it is expected that they will also be targets of nephrotoxicants that can ultimately lead to nephrotic syndrome, although no data are as of yet available on drug effects in this cell line (Sakairi et al. 2010).

Toxicity assays mainly focus on measuring cell death; however, renal toxicity can also be manifested by changes in cell polarity, membrane integrity, and mitochondrial function. With this in mind, Sjögren et al. developed a machine learning model that allowed screening of 62 drugs in which ciPTEC-OAT1 cell line was used to predict their nephrotoxicity based on multiple parameters (Sjögren et al. 2018). Similarly, Secker et al. made use of the RPTEC/TERT1 cell line to evaluate transepithelial transports in a small set of known nephrotoxic and non-nephrotoxic drugs, demonstrating that further evaluation of functional parameters, including transepithelial electrical resistance (TEER), reabsorption, and secretion of solutes, is essential to understand the nephrotoxicity mechanisms of drugs and predict the in vivo implication in regards to kidney performance (Secker et al. 2019).

Advanced in vitro models

To bypass the limitations of 2D cultures, advanced in vitro culture systems have been developed, including the use of 3D organized structures, known as organoids, and kidney microphysiological systems (MPS) that can recreate fluidic characteristics found in vivo (Fig. 4). Organoids can be cultured from different sources of stem cells, including embryonic stem cells (ESC), induced pluripotent stem cells (iPSC), and adult stem cells. Due to ethical concerns regarding the culture of embryonic stem cells, iPSCs and adult stem cells are preferred. Using human iPSC cells (Table 3), it is possible to generate kidney organoids that contain cell types from different nephron segments; however, the generated cells are not fully mature (Takasato et al. 2015). To overcome this problem, Chuva et al. developed a two-step protocol in which kidney organoids were transplanted into a chick chorioallantoic membrane to provide a vascularized environment that is necessary for the further maturation of the organoids (Chuva de Sousa Lopes 2019). Examples of other 3D culture systems include RPTEC/TERT1 and Nki-2 cells that, when cultured in Matrigel or Matrigel mixed with collagen I, respectively, were able to further mature and form tubular structures as seen in vivo. Both models showed increased sensitivity to known nephrotoxic drugs when compared to 2D cultures (Desrochers et al. 2013; Secker et al. 2017).

In line with these 3D culture systems, a bioengineered kidney tubule was developed that mimics the physiological geometry of the nephron segment. Briefly, ciPTEC-OAT1 cells were seeded onto polyethersulfone (PES) hollow fiber membranes (HFM; Table 3), previously double-coated with 3,4-dihydroxyl-L-phenylalanine (L-DOPA) and collagen IV. Using this system, the excretion of protein-bound uremic toxins and reabsorption of albumin were shown under perfusion conditions, thus mimicking the in vivo situation (Jansen et al. 2015, 2016b) and revealing a remote sensing and signaling pathway to balance microbial metabolite levels in the human body (Jansen et al. 2019). Furthermore, attenuation of uremic toxin-induced damage by vitamin D activated by the bioengineered kidney tubules was demonstrated (Mihajlovic et al. 2017). The use of decellularized kidneys (Table 3) can also be a suitable platform for studying drug-induced nephrotoxicity. Fedecostante et al. decellularized surplus rat kidneys using sodium dodecyl sulfate (SDS) and recellularized these with ciPTEC-OAT1. An increased sensitivity to cisplatin, tenofovir, and cyclosporin A was shown for this model as compared to the 2D system (Fedecostante et al. 2017).

For further improvement of these in vitro models, implementation of fluid flow and vasculature is crucial, not only to increase maturation of the kidney cells but also to provide an environment that more closely resembles the in vivo situation. Flow in tubular lumens varies between 0.2 and 2.0 dyne/cm^2 (Cai et al. 2000) and triggers mechanosensitive pathways via microvilli, primary cilia, and the glycocalyx, all expressed at the tubular apical membrane (Raghavan and Weisz 2016). Advances in microelectromechanical systems (MEMs) allowed researchers to apply microfluidics in cell and tissue cultures that resulted in the so-called

Table 3 In vitro models for toxicity screening

	Species	Characteristics	Pros	Cons	References
Primary					
RPTEC	Human	Morphology Cuboidal with a characteristic pattern of swirled cells Markers Complete expression of transporters and metabolic enzymes Function Active transepithelial transport function Polarized tight monolayer formation	Preserve genetic and phenotypic aspects of the tissue of origin Easy to isolate Compatible with high-throughput screening and advanced imaging techniques	Cell sourcing problems Inter-donor variability Functional changes during passages Low lifespan Low predictivity	Stray et al. (2013), Uetake et al. (2014) and Breda et al. (2019)
HRMC (mesangium)	Human	Markers Fibronectin, Thy-1, smooth muscle actin Study IgA nephropathy			Rodriguez-Barbero et al. (2000) and Liang et al. (2015b)
HRCEpiC (renal cortical)	Human	Markers Cytokeratin 18, 19, vimentin Function Production of IL-8 Inflammation (IL-2Ra and MHC II)			Schmouder et al. (1992) and Lee et al. (2014)
aProximate™	Human, rat, mouse	Morphology RPTEC Markers MDR1, MRP2/4, BCRP, OCTN1/2, OAT1/2/3/4, OCT2/3, OATP4C1 Function Net secretion of substrates Calcein efflux via MRP2 BCRP and MDR1 activity (Hoechst 33342 dye)			Brown et al. (2008a, b) and Jenkinson et al. (2012a)
Kidney slices	Human, rat, mice, dog	Retain the multicellular, structural, and functional features		Damage from cutting Heterogenous population	De Kanter et al. (1999; Kowalkowski et al. 2017) and Arakawa et al. (2017)
Isolated perfused kidney	Rat, mouse	Tubulovascular integrity		Short lifespan Lower levels of filtration rate and ion reabsorption Not suitable for routine studies	Georgiev et al. (2011)
Isolated perfused nephrons	Rat, rabbit	Knowledge on location of enzyme systems, metabolic pathways, and distribution of receptors		Not suitable for routine studies	Schafer et al. (1997)

Table 3 (continued)

	Species	Characteristics	Pros	Cons	References
Immortalized cell lines					
RPTEC/TERT1	Human	Morphology Functional tight junctions, dome formation, microvilli and primary cilium Markers Aminopeptidase-N, E-cadherin, MRP2, MRP4, OAT4, MDR1, MATE1, OCTN2, OCT3 Function Response to PTH treatment by increased cAMP levels Gamma glutamyl-transferase activity Megalin/cubilin transport system	Enhanced proliferative capacity Differences in morphology and function Possible inclusion of ECM Compatible with high-throughput screening and advanced imaging techniques Cost-effective	Absence of OAT1 and OAT3 anion importers	Aschauer et al. (2015), Wieser et al. (2008), Wilmes et al. (2015) and Secker et al. (2019)
ciPTEC	Human	Morphology Formation of tight junctions Markers Aminopeptidase-N, Pgp, AQP1, dpp-IV, MRP2/4, OCT2, OAT1, OAT3, BCRP, MATE1/2, CaSR, Megalin/Cubilin receptors Function ALP activity, Albumin endocytosis, sodium-dependent phosphate uptake, OCT2 and P-gp activity, UGT activity		Absence of SGLT2	Jansen et al. (2014), Nieskens et al. (2016) and Wilmer et al. (2010)
HK-2	Human	Morphology Cuboidal morphology, contact inhibition, dome formation, and microvilli Markers Vimentin, cytokeratin, α3β1 integrin, leucine aminopeptidase, fibronectin, MCT1, MDR1, OATP4C1 Function Gluconeogenesis, and Na^+-dependent glucose uptake GGT and alkaline phosphatase activity Increased cAMP levels in response to PTH Synthesis and secretion of plasma proteins		Does not represent a good model for the study of key renal uptake transporters Low predictivity	Ryan et al. (1994), Zhao et al. (2017), Jenkinson et al. (2012b) and Murphy et al. (2017)
Nki-2	Human	Epithelial and proximal tubule phenotype Markers E-cadherin, CK8/18/19, GGT1, OAT1, OAT4 Function Production of cAMP in response to PTH, ADH GGT and LAP activity Absorption of glucose in the presence of NaCl		Limited data available	Desrochers et al. (2013)
CIHP-1	Human	Morphology Foot processes, and slit-diaphragm-like structures Markers Synaptopodin, nestin, CD2AP, nephrin, podocin, WT1, podocalyxin, P-Cadherin, α, β, γ-catenin		Limited data available	Sakairi et al. (2010)

Table 3 (continued)

	Species	Characteristics	Pros	Cons	References
Stem cell-derived					
ESC/iPSC	Human	Markers N-cadherin, KSP-CAD, AQP1/2/3, Megalin/Cubilin, GLUT1, OCT2, MDR1, GGT, OAT1/3, PODXL, UMOD Function Citrin uptake by OAT1/3 (inhibited by probenecid)	Easy to isolate (iPSC) Possible inclusion of ECM Study molecular mechanisms of diseases Enables personalized medicine	Ethical issues (ESC) Low sensitivity Extensive protocol	Lam et al. (2014), Mae et al. (2013), Kandasamy et al. (2015) and Takasato et al. (2014)
Organoids	Human	Markers PODXL, WT1, LTL, E-cadherin, UMOD, SIX2, PAX2, JAG1 Function Transport of fluorescent compounds (lucifer yellow, rhodamine-conjugated dextran, fluorescein methotrexate)	Inclusion of ECM Heterogenous population Epithelial cell polarization Enables personalized medicine	Heterogenous population Difficult access to apical compartment Batch-to-batch variability of Matrigel	Xia et al. (2014), Freedman et al. (2015) and Takasato et al. (2015)
Others					
Kidney-on-a-chip	Human	Resemble kidney proximal tubules (tubular conformation and active transepithelial transport)	Increased physiological relevance (3D structures, ECM, multiple compartments) Exposure to fluid flow and sheer stress Suitable for studying transepithelial transport	Prototype Require external tube and pump connection Made of materials that absorb hydrophobic compounds Not suitable for routine studies	Jang et al. (2013), Wilmer et al. (2016), Weber et al. (2016), Lee and Kim (2018) and Schutgens et al. (2019)
Bioartificial kidney tubules	Human	Morphology and markers ciPTEC Function Polarized secretion of immune modulators (upon LPS stimulation) Transport of organic anions and cations Reabsorption of albumin Diffusion of FITC-Inulin	Inclusion of ECM Epithelial cell polarization Suitable for studying transepithelial transport Exposure to fluid flow and sheer stress	Only basolateral perfusion Low–high throughput Not suitable for routine studies	Jansen et al. (2015, 2016a) and Chevtchik et al. (2018)
Decellularized kidney	Rat	Recellularization ciPTEC Markers ZO-1, AQP1, CLDN-2, OCT2, MATE-1, MATE-2K, OAT1, MRP4, P-gp, BCRP, GLUT1, OATP4C1 Function OCT2 activity (ASP^+)	Native scaffold Improved cell function	Homogenous cell population No fluid shear stress included	Fedecostante et al. (2018)

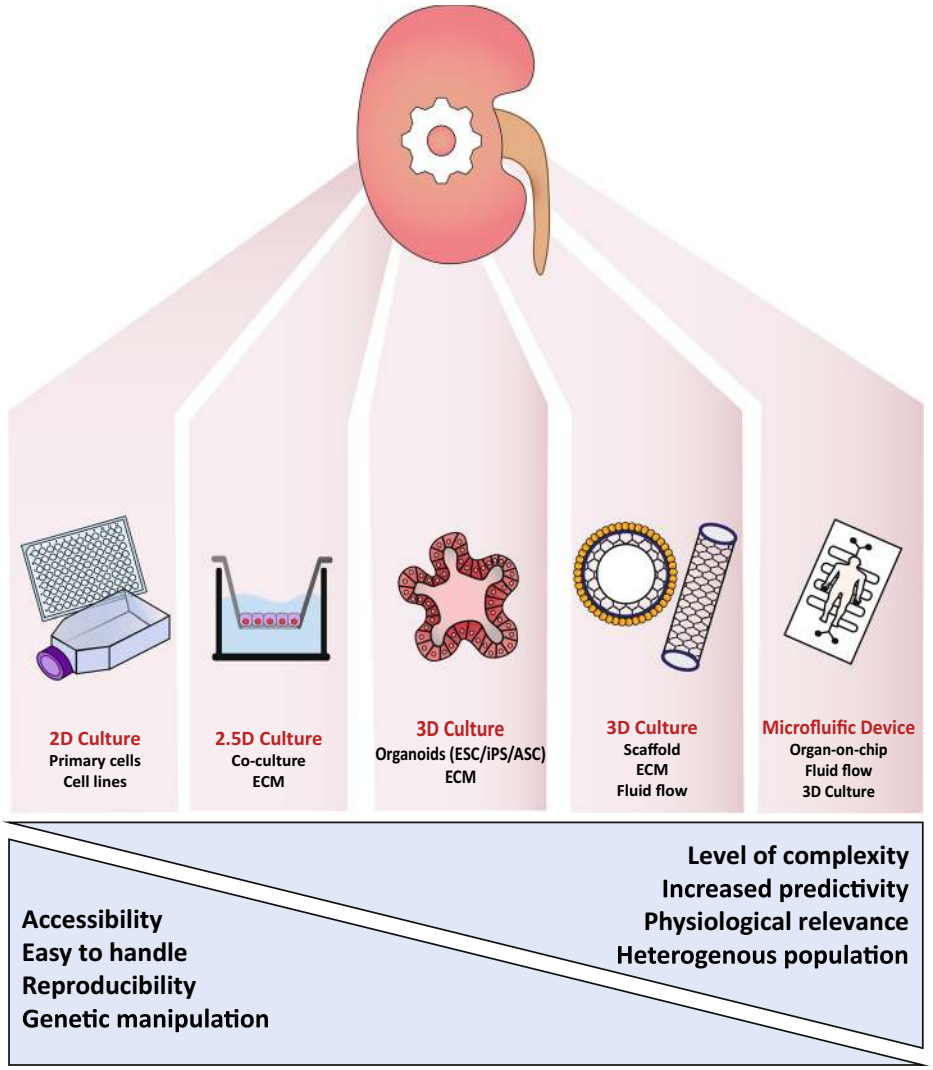


Fig. 4 Schematic figure of the different in vitro models developed for use in nephrotoxicity screenings

organ-on-a-chip (Table 3). Vriend et al. demonstrated that culturing ciPTEC-OAT1 in an OrganoPlate, a 3D platform consisting of 96 chips that provides fluid shear stress by placing the plate on a rocker platform, it was possible to create a high-throughput screening method compatible with advanced imaging techniques (Vriend et al. 2018). Following a similar approach, Schutgens et al. developed a new microfluidic in vitro system using kidney tubular epithelial organoids, or "tubuloids", derived from adult stem cells. The generated tubuloids showed active transepithelial transport function and were used to model several diseases, including BK virus, Wilms tumor, and cystic fibrosis, showing the great potential of this culture system for disease modeling and the possibility to use it for drug screening (Schutgens et al. 2019).

A lack of vascularization could potentially be overcome by the use of a 3D-print chip that combines hPSC-derived kidney organoids co-cultured with glomerular microvascular endothelial cells (GMECs) in a gelatin-fibrin ECM, as recently reported (Homan et al. 2016, 2019). The researchers showed an improved maturation of the kidney organoids when cultured under flow and in the presence of vascularization. Later, the same microfluidic platform was used to study active reabsorption of solutes between proximal tubule epithelial cells and vascular epithelium, and for the study of hyperglycemic conditions.

As mentioned before, the kidney also interacts with and reacts on remote organs. The liver and the kidney are two very complex organs that together lead to the metabolism and excretion of drugs, respectively. To predict biotransformation (liver) and elimination (kidney) in humans is a rather difficult task to achieve using normal 2D cultures (Chang et al. 2016); however, the combination of these two complex organs in an organ-on-a-chip platform made it possible to study the toxic effects of aristolochic acid I, a well-known nephrotoxicant that requires first hepatic bioactivation (Chang et al. 2017). Table 3 summarizes the different in vitro models discussed to study drug-induced

nephrotoxicity. Together, the findings suggest that the development and use of advanced in vitro kidney models are important improvements in renal drug safety assessment.

Perspectives in in vitro models' development

Renal clearance is an important route of drug elimination from the bloodstream, mainly facilitated by the proximal tubule, which renders proximal tubule epithelial cells prone to drug-induced kidney injury. Mimicking the in vivo environment by including extracellular matrix (ECM) components, three-dimensional (3D) architectural features, a heterogeneous cellular composition and incorporating fluid shear stress in an in vitro kidney model could improve prediction of injury after drug exposures. These features need to be taken into consideration when trying to develop new in vitro models. The complex renal ECM, recently reviewed in (van Genderen et al. 2018), is in constant remodeling, especially in the transition of healthy to disease state, such as fibrosis. As fibrosis affect the different compartments of the kidney, a comprehensive analysis of the renal ECM is crucial to study the pathophysiology of the disease and its specific biomarkers (Bülow and Boor 2019). As stated before, shear stress triggers mechanosensitive pathways via microvilli, cilia, and the glycocalyx. Understanding how these structures coordinate with each other in response to flow will broaden our knowledge and help identify new molecular targets of diseases (Raghavan and Weisz 2016). Combining these features in a 3D model that includes tubule curvature (Yu et al. 2018) will allow for a better cell polarization and enhanced expression of cell markers.

Currently, in pre-clinical safety assessment studies, only a limited number of drug candidates (2–8%) are being rejected because of nephrotoxicity (Cook et al. 2014; Guengerich 2011). A survey among pharmaceutical companies showed that the majority of drug candidates displaying nephrotoxicity in clinical trials did not show nephrotoxicity in preclinical trials (Troth et al. 2019). It is thus apparent that the currently used strategies to predict drug-induced injury warrant strong improvements. Immortalized cell lines, like ciPTEC, represent a steady and reproducible cell source for in vitro models, but are derived from one single donor and show significant changes in cell function and morphology compared to primary cells (Astashkina et al. 2012). Baseline levels of injury marker KIM-1 were 20-fold higher in immortalized cells compared to primary cells (Sakolish et al. 2018). In addition, immortalized cell lines often show chromosomal instability, as demonstrated for ciPTEC-OAT1 without affecting cell function or posing a tumorigenic risk (Mihajlovic et al. 2019), and represent a homogenous population instead of a genetic diverse population. Therefore, new sources for kidney cells emerged in the past decade. Stem cell-derived tubular cells can be obtained from multiple donors and may have potential for studying nephrotoxicity in a heterogeneous population (Wnorowski et al. 2018). Well-defined protocols to establish kidney organoids of renal tubular epithelial cells from induced pluripotent stem cells (iPSCs) derived from fibroblasts are now available (Czerniecki et al. 2018; Freedman et al. 2015; Kaminski Michael et al. 2016; Morizane et al. 2015; Takasato et al. 2015). In these cultures, typical proximal tubule cell characteristics have been demonstrated, such as albumin uptake, expression of tight junction proteins, expression of OAT1, microvilli, and apical and basolateral membrane polarization. In addition, cytotoxicity was demonstrated using cisplatin (Czerniecki et al. 2018; Freedman et al. 2015; Kaminski Michael et al. 2016; Morizane et al. 2015; Takasato et al. 2015), gentamicin (Freedman et al. 2015; Kaminski Michael et al. 2016; Morizane et al. 2015), tacrolimus (Kaminski Michael et al. 2016), and adriamycin (Kumar et al. 2019). As earlier stated, kidney tubuloids grown from adult stem cells (ASCs) are another promising approach as they allow for long-term culturing and better maturation without losing chromosomal stability (Schutgens et al. 2019).

To model kidney diseases, direct pathogen exposure and genome editing have been applied, depending on the cause of disease. Effects of Shiga toxin 2, a cytotoxic protein causing hemolytic-uremic syndrome (HUS), were studied in a 3D model of renal cortical epithelial cells (DesRochers et al. 2015). And polycystic kidney disease was studied via CRISPR-Cas9 genome editing of PC-1 and -2 in iPSC-derived kidney organoids (Czerniecki et al. 2018; Freedman et al. 2015). Personalized medicine allows for studying disease progression and testing treatment options in a tailor-made fashion via obtaining tissue from kidney disease patients. ASCs-derived tubuloids from Wilms tumors elucidated an important role for SIX2, a kidney development marker (Kobayashi et al. 2008; Schutgens et al. 2019). Furthermore, tubuloids obtained via urine from cystic fibrosis patients were used to assess treatment efficacy and circumvented the use of an invasive method to obtain patient material (Schutgens et al. 2019). Furthermore, the dynamic process of kidney stone formation was studied in HK-2 cells cultured in a microfluidic device, which allowed real-time monitoring of calcium phosphate deposition in the lumen (Wei et al. 2012).

Improving predictability of in vitro models fits also in the scope of the 3Rs (replacement, reduction, refinement) of animal experiments. This could reduce costs of the preclinical and clinical phases of drug development by filtering out the harmful compounds. However, more importantly, it also meets the societal demands to reduce the number of animals in drug development. Drug regulatory authorities, such as FDA and EMA, support the use of physiologically based pharmacokinetic (PBPK) modeling as a tool to facilitate the process of drug development. In vitro-to-in vivo

extrapolation (IVIVE) can be coupled with PBPK modeling as a way to predict the in vivo pharmacokinetic characteristics of a new drug based on in vitro studies. In vitro studies can provide information regarding drug–enzyme and drug–transporter interactions. However, the full understanding of the absorption, distribution, metabolism, and excretion (ADME) processes is not feasible. By extrapolating complex scenarios observed in vitro while having in mind that intrinsic and extrinsic factors can alter the kinetic values, one can identify optimal dosing regimens for individual patients (Rostami-Hodjegan 2012; Zhao et al. 2011; van der Made et al. 2019).

Conclusions

Nephrotoxicity is associated with significant mortality and morbidity. Undoubtedly, drug-induced nephrotoxicity is a major cause of renal impairments and a potential impediment to the research and development of drugs, requiring more reliable and early diagnosis to avoid potentially fatal chronic conditions. To date, there is no ideal kidney-based in vitro model for the study of nephrotoxicity; however, we are moving towards more advanced in vitro culture systems that offer great promise for the assessment of drug toxicity. These new models include several characteristics that are important for the successful toxicologic read-out of drug candidates, including 3D architectural features, ECM components, fluid flow, and multiple cell types combined. Despite the promising advances of these models, appropriate toxicity end-points and sensitive translational biomarkers are yet to be identified. Current efforts remain as "bench-work" and do not reach the "bed-side". Therefore, there is a pressing need to systematically combine in vitro, in vivo, and clinical inspections to develop a panel of safety biomarkers that can effectively and reliably diagnose and monitor renal function, damage, and recovery.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest with the contents of this article.

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