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In vitro models in studying nephropharmacology

Renal fibrosis in precision-cut kidney slices

Elisabeth G.D. Stribos [a,b], Jan-Luuk Hillebrands [c], Peter Olinga [a,*], Henricus A.M. Mutsaers [a]

[a] Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Groningen Research Institute of Pharmacy, The Netherlands
[b] Department of Internal Medicine, Division of Nephrology, University of Groningen, University Medical Center Groningen, The Netherlands
[c] Department of Pathology and Medical Biology, Division of Pathology, University of Groningen, University Medical Center Groningen, The Netherlands

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ABSTRACT

Chronic kidney disease (CKD) is associated with renal fibrosis, a pathological process that is characterized by excessive accumulation of extracellular matrix proteins resulting in loss of organ architecture and function. Currently, renal transplantation and dialysis are the sole treatment options for advanced CKD, yet these therapies have limited impact on fibrogenesis. Even though antifibrotic therapies are being developed, the search for effective antifibrotic drugs is being hampered by the lack of appropriate cell and animal models to study renal fibrosis. *In vitro* models lack cellular heterogeneity whereas *in vivo* models do not fully reflect human pathology. Precision-cut tissue slices, prepared from human or rodent tissue, provide a unique *ex vivo* model system that captures the complexity of organs, and they are widely used for ADME/Tox drug testing. Moreover, precision-cut kidney slices (PCKS) have been recently established as a useful model to study renal fibrosis. This review summarizes the currently available models for renal fibrosis, describes the wide array of possibilities with PCKS and shows its role in the search for antifibrotic drugs.

1. Introduction

The kidneys play an important role in maintaining total body homeostasis and the complexity of this task is reflected by the unique architecture of the organ, which consists of glomeruli, the tubular system, interstitium and vasculature. Injury caused by trauma, infection, ischemia or systemic disease can lead to injury at any of these sites and this will often result in a disruption of the physiological balance between extracellular matrix (ECM) production and degradation (Decleves and Sharma, 2014; Mutsaers et al., 2015). When ECM production is favored, damaged renal tissue will be replaced by acellular and collagen-rich scar tissue thereby diminishing the functionality of the kidney. These lesions in the kidney are characterized by glomerulosclerosis, tubular atrophy, tubulointerstitial fibrosis and intima hyperplasia (Boor et al., 2010), more generally termed renal fibrosis. The pathogenesis of fibrosis is extremely complex involving a variety of resident and circulating cells as well as several molecular signaling pathways (Boor et al., 2010). Transforming growth factor β (TGF-β), platelet derived growth factor (PDGF) and connective tissue growth factor have been identified as quintessential players in the fibrotic process in most organs (Eddy, 2014; Kok et al., 2014). After the initial injury, these pathways synergize with each other to promote fibrosis and activate profibrotic cells (Wang et al., 2011). (Myo)fibroblasts, *i.e.* ECM-producing cells, make up the majority of the renal interstitial cell population (Zeisberg and Kalluri, 2015) and they are key players in the fibrotic process. However, molecular markers to discern mesenchymal stromal cells, resident fibroblasts and activated fibroblasts remain elusive, hampering the study of these cells and their specific roles in health and disease (Thedieck et al., 2007; de Almeida et al., 2016). They can however be recognized by their spindle-shaped morphology and their abundance of rough endoplasmic reticulum. Resident fibroblasts can acquire the phenotype of profibrotic myofibroblasts as a response to epithelial or endothelial injury resulting in an increased synthesis of ECM (mostly collagen I, III and fibronectin; (Liu, 2011; Zeisberg and Neilson, 2010)). Other precursor populations of pathological myofibroblasts have been identified over the last years including pericytes, bone-marrow-derived cells and cells originating from either epithelial- or endothelial-to-mesenchymal transition (EMT and EndoMT; Mack and Yanagita, 2015; Falke et al., 2015; LeBleu et al., 2013; Kramann et al., 2013). However, the origin of renal myofibroblasts remains debated, and there exists considerable controversy as to the role of cellular transition in the ontogeny of these cells (Kriz et al., 2011). Yet, consensus is arising that renal myofibroblasts arise from FOXD1-lineage cells, which give rise to stromal and mural cells of the kidney (Duffield, 2014).

Renal fibrosis is the final deleterious outcome of several chronic kidney diseases (CKD). Currently, the incidence of CKD is rising,

* Correspondence to: University of Groningen, Department of Pharmaceutical Technology and Biopharmacy, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands.
E-mail address: p.olinga@rug.nl (P. Olinga).

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which has a substantial impact on health care budgets due to the high prevalence of morbidity and mortality associated with CKD (Couser et al., 2011; Jha et al., 2013). Unfortunately, the sole treatment options for advanced CKD, *i.e.* end-stage renal disease (ESRD), are dialysis and transplantation. Since the fibrotic process is highly intertwined with the development and progression of CKD many therapeutic options have been investigated in hopes of slowing down or even reversing fibrosis (Cernaro et al., 2014). Although several studies have been successful at the pre-clinical level, only limited advances have been made at this time in the translation of these findings to the level of patient treatment (Lee et al., 2015; Mutsaers et al., 2015).

The search for antifibrotic drugs is impeded by the lack of appropriate cell and animal models to study human renal fibrosis. *In vitro* studies lack cellular heterogeneity, which is a prerequisite to mimic the multicellular character of fibrosis, while results from animal experiments often do not match the human situation, and differ per strain within a given species (Inoue et al., 2015). Precision-cut kidney slices (PCKS) might be an extremely useful model to elucidate the process of renal fibrogenesis and to accelerate the search for effective antifibrotics. This review summarizes the currently available models for renal fibrosis, describes the wide array of possibilities with PCKS and shows its role in the search for antifibrotic drugs.

2. Models of kidney fibrosis

2.1. In vitro models of renal fibrosis

Cell culture is a simple, cost-efficient and potential high-throughput method to study fibrosis (Desrochers et al., 2014). Consequently, a myriad of studies use primary or immortalized human cells to elucidate the different aspects of fibrogenesis. In general, either fibroblasts or proximal tubular epithelial cells, *e.g.* HK-2 cells, are used. Unfortunately, some of these cells do not fully reflect normal renal physiology (Jenkinson et al., 2012; Mutsaers et al., 2011). Moreover, this experimental method fails to replicate the multicellular feature of fibrosis as well as the complex 3D architecture of the kidney (Desrochers et al., 2014). To tackle the latter, 3D tissue engineered disease models are being developed using, amongst others, hydrogels, decellularized kidneys or organ-on-a-chip technology (Desrochers et al., 2014). However, these models face many technical hurdles and advancement is also dependent on the possibility to obtain functionally relevant and genetically accurate renal cell lines (Desrochers et al., 2014). Additionally, in order to study cell-cell interactions and to minimize the gap between cell culture and the *in vivo* situation, co-culture models have been developed (Dixon et al., 2014). Still, at this time, the usefulness of cell culture models to study renal fibrosis are limited, yet they are very helpful to understand single cell behavior in this pathological process.

2.2. In vivo models of renal fibrosis

Our current understanding of renal fibrosis is for a large part derived from animal studies. In the last decades, a wide variety of models have been established to study renal fibrosis using surgical interventions or the administration of toxic substances to initiate fibrogenesis. The three most widely used surgical models are: unilateral ureteral obstruction (UUO; (Klein et al., 2011; Chevalier et al., 2009)), subtotal nephrectomy (Ma and Fogo, 2003) and renal ischemia and reperfusion (Eddy et al., 2012). Chemically, renal fibrosis can be induced by antiserum (Tam et al., 1999), adriamycin (Lee and Harris, 2011), angiotensin II (Flamant et al., 2006; Liu et al., 2012) and a myriad of other compounds. Furthermore, fibrosis can also be induced by a high salt diet resulting in hypertension. In addition, a genetically modified mouse strain, COL4A3$^{-/-}$, with a phenotype resembling Alport syndrome, is associated with renal fibrosis (Gross et al., 2010). Unfortunately, the major disadvantage of all these models is that the obtained results differ per strain (Inoue et al., 2015), and the experiments are associated with considerable discomfort for the animals. Still, animal models have the advantage over cell culture since they allow for the study of renal fibrosis on a systemic level, yet translation to the human situation remains difficult.

2.3. PCKS as an ex vivo model of renal fibrosis

PCKS provide a unique *ex vivo/in vitro* model in which cellular heterogeneity and organ architecture is maintained. This makes the model very useful to elucidate multicellular pathological processes including fibrosis. Recently, Poosti et al. successfully used murine PCKS to study renal fibrosis as well as the antifibrotic effect of interferon γ (IFNγ) and a IFNγ conjugate targeted to the PDGF-β receptor (PPB-PEG-IFNγ). To improve the application of PCKS to study human disease, Stribos et al. (2015) prepared slices from human tissue obtained from tumor nephrectomies and provided an in-depth characterization of human PCKS demonstrating that the slices maintained their renal phenotype during long-term culture, and that the model can be used to study the early onset of renal fibrosis. Thus, PCKS could serve as a translational model bridging the gap between *in vitro* studies and clinical trials.

3. Precision-cut kidney slices

3.1. History of precision-cut tissue slices

The use of tissue slices for (patho)physiological research dates back to 1923, when Otto Warburg invented the use of slices to study cancer cell metabolism (Warburg, 1923; Koppenol et al., 2011). The technique was however not well optimized and the tissue slices were hand-cut with a razor blade. Decades later, Carlos Krumdieck developed a semiautomatic slicing machine leading to a revival of the popularity of the tissue slices technique in 1980 (Krumdieck et al., 1980). Because of the technical improvement of the methodology it is now possible to make accurate and reproducible tissue slices from (solid) organs from a variety of species including humans. To this day, the quality of precision-cut tissue slices (PCTS) is being improved by optimizing preparation and incubation settings (de Graaf et al., 2010), also in the field of tumor biology (Davies et al., 2015) for which Otto Warburg initially developed the method. All in all, the technique has made great progress and PCTS are now widely used to study drug metabolism (Niu et al., 2015; Elferink et al., 2011; van Midwoud et al., 2011a, 2011b), drug toxicity (Niu et al., 2014; Hadi et al., 2013; Iswandana et al., 2016; Elferink et al., 2008), drug efficacy (Westra et al., 2014a; Westra et al., 2016) and fibrosis (Pham et al., 2015; Westra et al., 2014b; Poosti et al., 2015; Stribos et al., 2015).

3.2. Precision-cut kidney slices: the technical aspects

The preparation of PCKS is illustrated in Fig. 1. In short, human renal tissue is obtained from kidneys that had to be surgically removed due to a renal cell carcinoma. Subsequently, cores are made with a biopsy punch using only macroscopically healthy parts of the kidney. For murine PCKS, kidneys are collected via a terminal procedure performed under isoflurane/O_2 anesthesia. From here on, the method to prepare either murine or human PCKS is identical. PCKS are obtained using the Krumdieck tissue slicer and the slices are subsequently cultured in William's E

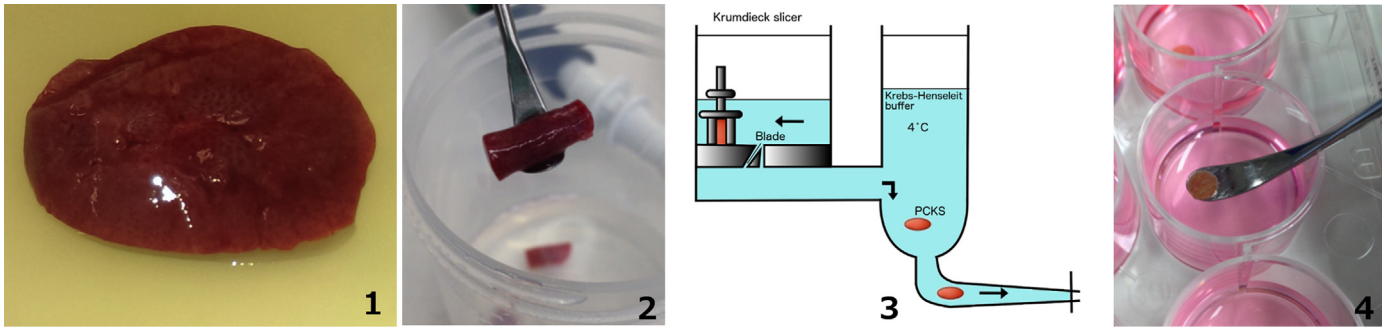

Fig. 1. Workflow preparation precision-cut kidney slices. Cylindrical cores, 6 mm in diameter, were obtained from human renal cortical tissue using a biopsy punch (Step 1, 2). PCKS were prepared using the Krumdieck tissue slicer, slices with a wet weight of 4–6 mg had an estimated thickness of 250–300 μm (Step 3, 4). Slices were subsequently incubated in optimized medium at 37 °C and 80% O_2, 5% CO_2 in an incubator shaking at 90 rpm (amplitude 2 cm).
From Stribos et al. (2015); used with permission from Elsevier.

medium containing *inter alia* ciprofloxacin at 37 °C in a 80% O_2, 5% CO_2 atmosphere while gently shaken. PCKS can be cultured up to 72 h for human slices and up to 48 h for murine PCKS during which time tubular functionality is maintained. A detailed material and methods section can be found in the original articles (Stribos et al., 2015; Poosti et al., 2015).

3.3. Characteristics of precision-cut kidney slices

Human PCKS have been used for several decades, especially for drug metabolism studies (De Kanter et al., 2002; Vittorelli et al., 2004; Connors et al., 1996). However, in these studies, slices were only cultured for 24 h and detailed characterization of PCKS following long-term incubation was absent. Recently, our group demonstrated that the viability of human PCKS can be maintained in culture up to 72 h, based on morphology, ATP levels and LDH leakage. Furthermore, experiments testing uridine 5′-diphosphoglucuronosyltransferase and transporter activity in PCKS revealed renal metabolic activity up to 48 h. We also observed an inflammatory response in PCKS at the start of culture (0–24 h) followed by a fibrotic response (48–72 h). Moreover, the fibrogenic response can be augmented via treatment with the archetypical profibrotic factor TGF-β1 (Stribos et al., 2015).

A multitude of read-out parameters can be used in PCKS experiments. Some basic techniques for viability such as ATP, LDH leakage and morphological analysis have been thoroughly studied (Baverel et al., 2013; Poosti et al., 2015; Stribos et al., 2015; Vickers et al., 2004; De Kanter et al., 2002). Protein and gene expression have been measured in PCKS by immunohistochemical staining, western blot, ELISA, HPLC, ^{13}C NMR, qPCR and microarray analysis (Poosti et al., 2015; Vickers et al., 1995, 2004; Stribos et al., 2015; Baverel et al., 2013; Vittorelli et al., 2005; De Kanter et al., 2002). Taken together, PCKS can be used to study the molecular mechanisms of renal diseases, for ADME/Tox drug testing and drug discovery.

3.4. Use of PCKS in (nephro)pharmacological research

PCKS have already been demonstrated to be useful for pharmacotoxicology studies (de Kanter et al., 2002b), especially to unravel mechanisms of (site-specific) nephrotoxicity (Baverel et al., 2013). To illustrate, Vickers et al., studied the impact of cisplatin, a chemotherapeutic agent with known nephrotoxic effects, on human kidney slices and clearly demonstrated site-specific toxicity with widespread tubular necrosis, while the glomeruli appeared unaffected (Vickers et al., 2004). Moreover, exposure to cisplatin induced gene expression changes in genes associated with, amongst others, DNA damage, growth arrest, protein damage, intracellular signaling and calcium homeostasis (Vickers et al., 2004). Furthermore, using rat PCKS, it was demonstrated that chloroacetaldehyde, one of the main metabolites of the cystostatic drug ifosfamide, elicited nephrotoxicity by inhibiting the activity of complex I of the mitochondrial respiratory chain as well as gluconeogenesis (Knouzy et al., 2010). In another interesting study, although using hand-cut slices of ~0.5 mm thickness, Dickman et al., investigated the toxicity of aristolochic acid I (AA), a compound produced by *Aristolochia* (*i.e.* birthwort) plants that specifically targets the proximal tubule and that is known to cause AA nephropathy (Dickman et al., 2011). Of note, enzymatic nitroreduction of AA generates a reactive nitrenium intermediate capable of forming DNA adducts. Using murine renal cortical slices, Dickman et al., demonstrated the formation of DNA adducts following treatment with AA, which could be mitigated by probenecid, a potent inhibitor of organic anion transporters (Dickman et al., 2011). Thus, PCKS can be used to unravel complex mechanisms of (drug-induced) toxicity.

3.5. PCKS: a model to study renal fibrosis

As reported previously, renal fibrosis can be induced in PCKS by either culture activation or treatment with TGF-β1 allowing us to study the early onset of fibrosis (Zhang et al., 2016; Stribos et al.,

Table 1
Fibrosis-related changes observed in PCKS.

PCKS fibrosis model		TGF-β pathway	PDGF subunit B	COL1A1	FN1	HSP47	α-SMA	Ref
Human	Culture activation	↑(late)	↑ (early)	↑	↑	–	–	(Stribos et al., 2015)
	TGF-β1	↑	ND	↑	↑	↑	↑	
Mouse	TGF-β1	ND	ND	↑	↑	ND	↑	(Poosti et al., 2015)
	TGF-β1	↑	ND	ND	ND	ND	ND	(Zhang et al., 2016)
Rat	UUO	↑	ND	↑*	ND	ND	↑	(Genovese et al., 2016)

↑, increased activity/expression; -, no difference; ND, not determined; TGF-β, transforming growth factor β; PDGF, Platelet-derived growth factor; COL1A1, alpha-1 type I collagen; FN1, fibronectin 1; HSP47, heat-shock protein 47; α-SMA, α-smooth muscle actin; UUO, unilateral ureteral obstruction.

* Increased collagen type I remodeling.

2015; Poosti et al., 2015). An overview of the fibrosis-related changes observed in rodent and human PCKS is summarized in Table 1. Fibrosis in human PCKS was studied by Stribos et al., demonstrating an increase in collagen type 1A1 and fibronectin 1 gene expression, as well as elevated protein levels of collagen type 1 (Stribos et al., 2015). Moreover, we observed a marked increase in the gene expression of both TGF-β1 and PDGF subunit B, two important factors involved in fibrogenesis. In addition, Poosti et al., studied fibrosis and antifibrotic drug targeting using murine PCKS (Poosti et al., 2015). They demonstrated a clear fibrotic response following treatment with TGF-β1 reflected by an increase in α-smooth muscle actin, fibronectin and collagen I mRNA and protein levels. Furthermore, TGF-β1-induced fibrosis could be mitigated by IFNγ and an IFNγ conjugate targeted to the PDGF-β receptor (PPB-PEG-IFNγ). The latter was developed by the authors to overcome the undesirable systemic effects and short half-life of IFNγ. This conjugate specifically targets the PDGF-β receptor and therefore targets activated myofibroblasts. Recently, Zhang et al. (2016) provided a more detailed description of the TGF-β pathway activity in murine PCKS. They showed that treatment with TGF-β1 resulted in an upregulation of p-Smad2, p-Smad3, p-ERK1, p-ERK2 and p-p38 MAPK in murine PCKS, which is in line with observations made in other models. However, all the aforementioned studies only investigated the early onset of fibrosis. To elucidate the pathophysiology of the final stages of the disease, PCKS prepared from fibrotic tissue are needed. In addition, such a model could be used to identify therapeutic targets for established renal fibrosis. To this end, the first studies are currently being performed in our lab using kidney slices from UUO mice. Recently, Genovese et al., demonstrated the feasibility of such an approach by preparing PCKS from UUO rats (Genovese et al., 2016). Using this model, they showed increased marker levels of collagen type I formation (P1NP), collagen type I and III degradation (C1M and C3M), as well as elevated levels of TGF-β1 and α-smooth muscle actin in PCKS supernatants (Genovese et al., 2016). To further improve translation, human fibrotic tissue can be used which could be obtained when the diseased (native) kidney is surgically removed during transplantation or following long-term graft loss. Unfortunately, both procedures are rare since it is common practice to leave the diseased kidney in the body during a transplantation procedure. Thus, an appropriate human model for established renal fibrosis still needs to be developed.

3.6. Role of PCKS in antifibrotic strategies

As stated previously, PCKS are a valuable tool to study antifibrotic strategies and to identify therapeutic targets. A myriad of putative antifibrotic compounds have already been tested in liver and intestinal slices, and is has been demonstrated that PCTS have good prognostic potential regarding drug efficacy in human disease (Westra et al., 2014b; Iswandana et al., 2016). To illustrate, using precision-cut liver slices (PCLS) prepared from rat and human tissue, we could clearly demonstrate species-specific effects of imatinib (Westra et al., 2016). This compound showed promising antifibrotic effects in animal studies as well as in rat PCLS. Yet, imatinib failed in clinical trials focusing on liver fibrosis, and also in human PCLS we could not observe any antifibrotic activity of this compound (Westra et al., 2016). Thus, PCTS have proven to be a valuable tool in the search for therapeutic options to treat fibrosis.

4. Future perspectives

The model of PCKS has been around for several decades, yet the technique is continuously evolving which foreshadows some exciting times to come. In the near future, a multitude of changes will likely establish this promising technique as an innovative replacement for experimental animal models. Therefore, PCKS promises to be an important tool to unravel renal fibrosis and unveil effective therapeutic options.

A limitation of PCKS in the study of renal fibrosis pertains to the fact that circulating inflammatory cells, which play a role in fibrogenesis (Meng et al., 2014), are not included in the experimental set-up. Moreover, during CKD there is a close interaction of renal and cardiac dysfunction (Mutsaers et al., 2015), and it has been speculated that other organs such as the liver, heart and intestines contribute to the development of renal fibrosis. To circumvent this problem, one could study interorgan interactions by using microfluidic biochips (van Midwoud et al., 2010). With this technique, human PCKS can be incubated in the microchamber of the microfluidic device, connected in series with a microchamber containing cell lines or precision-cut tissue slices.

Another future improvement would be to develop live imaging techniques using PCKS. Mishra et al., described the use of specific fluorescent labeling with a dye or the use of transgenic mice expressing a fluorescent reporter to study cerebral circulation in brain slices (Mishra et al., 2014). A major advantage of such a technique is that the fibrotic process can be studied in real-time during the complete culture period.

5. Discussion and conclusion

In conclusion, the technique of PCKS is underway to become a unique tool to study renal fibrosis. Already, a solid foundation has been provided with in-depth PCKS characterization and the successful use of PCTS in ADME/Tox and drug testing. With this novel model for renal diseases, the quest for antifibrotic therapies can be accelerated which will be extremely beneficial for CKD patients.

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