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Tissue-engineered kidney disease models ☆

Teresa M. DesRochers, Erica Palma, David L. Kaplan *

Department of Biomedical Engineering, Tufts University, Medford, MA, USA

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ABSTRACT

Renal disease represents a major health problem that often results in end-stage renal failure necessitating dialysis and eventually transplantation. Historically these diseases have been studied with patient observation and screening, animal models, and two-dimensional cell culture. In this review, we focus on recent advances in tissue engineered kidney disease models that have the capacity to compensate for the limitations of traditional modalities. The cells and materials utilized to develop these models are discussed and tissue engineered models of polycystic kidney disease, drug-induced nephrotoxicity, and the glomerulus are examined in detail. The application of these models has the potential to direct future disease treatments and preclinical drug development.

Contents

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* Corresponding author. Tel.: (617) 627 3251
E-mail address: david.kaplan@tufts.edu (D.L. Kaplan).

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1. Introduction

Tissue engineering can be broadly defined as the application of engineering principles to biological systems. A fundamental goal of tissue engineering is the regeneration of damaged or diseased organs which has been significantly advanced towards clinical use for organ systems such as skin, bone, bladder, and cartilage [1]. However, the regeneration of more challenging organs, such as the kidney, is not as advanced due to the complex composition and highly controlled functionality of the kidney. As such, the current strategy towards kidney tissue regeneration has focused on the development of simple building blocks that consist of a single cell type in a three dimensional (3D) environment *in vitro*. These simplified tissues are currently being applied to *in vitro* modeling of kidney diseases such as polycystic kidney disease (PKD), preclinical drug screening for nephrotoxicity, and understanding early kidney development. While these tissue engineered models will not replace the traditional experimental methodologies of 2D cell culture and animal models, they can provide relevant information that may compensate for the limitations of those methodologies. In this review, we summarize the techniques utilized to form tissue engineered kidney disease models and examine the models being developed to study PKD and drug-induced nephrotoxicity (DIN) and other kidney diseases (Table 1). While this review will focus primarily on the tubule region of the nephron, where the bulk of previous work has been concentrated, we will conclude with a discussion of the steps being made towards developing disease models of the glomerulus.

2. Why tissue engineering?

Traditionally, human disease has been studied using human patients, animal models, and cells cultured two-dimensionally (2D) on plastic dishes in the laboratory. These modalities have all contributed significantly to the understanding of kidney diseases such as PKD and DIN. However, these modalities have limitations which need to be compensated for in order to continue the progression of our understanding of kidney diseases and the development of more effective, less toxic therapies.

Studying kidney disease in human patients through patient clinical information is the gold standard for studying human diseases as it allows for exact replication of patient physiology, genetics, and environment. However, this approach has significant limitations. Patient data often represents the later or end stages of disease, can vary drastically between patients due to a plethora of uncontrollable genetic and environmental factors resulting in the need for very large sample sizes, and is subject to the availability and willingness of patients to divulge information and/or allow tissue biopsies. Additionally, since genetic and biochemical experimentation on humans is rarely an option, the acquired data is often limited to patient observation and screening. Tissue engineered kidney models offer the possibility of examining the early stages of disease progression by using human cells in a traceable, controlled environment. The use of human cells in these models and the ability to manipulate the environment and genetics of these cells allows scientists to better understand the factors involved in the development of disease phenotypes.

Animal models are commonly used as a replacement method for the study of disease in humans. They provide a more controllable experimental system compared to human patients while still maintaining both the overall complexity of *in vivo* physiology and the organization of cells and other factors within organ systems. However, animals vary significantly from humans in terms of gene expression and physiology and the extremely controlled nature of animal experiments are not representative of human life [2]. These limitations often make it difficult to translate animal experimental results to human treatments [3]. Animal experiments are also expensive relative to 2D cell culture, highly regulated, and pose numerous ethical issues. Recently, the ethical principle of the 3Rs, replace, refine, and reduce, for animal experimentation has undergone a major push by the European Union and is also beginning to make significant progress in the United States [4]. The replacement of animal models with tissue engineered models has achieved progress in the European Union where cosmetic testing on animals has been replaced by the use of engineered skin models [5]. Meanwhile, funding agencies within the United States have recently made a push for the development of tissue engineered models of human organs for preclinical drug testing. Although these systems will not be used to completely replace animals in drug testing, they will contribute to a reduction in the number of animal studies performed and have the potential to generate significant experimental results.

Unlike animal models, 2D cell culture of human cells provides human data in easily exploitable, genetically controlled environments. This experimental methodology is simple, low in cost, and potentially high-throughput thus enabling the testing of numerous conditions and/or treatments in relatively short timeframes. However, cells in 2D

Table 1
Comparison of different tissue engineered kidney disease models.

Disease	Cell source	Reference
Polycystic kidney disease	MDCK	[44,84–87,89,91–93]
	Mouse	
	Immortalized collecting duct	[94]
	PKD1$^{null/null}$ embryonic kidney with fibroblasts	[13,98]
	Inner medullary collecting duct cells	[58]
	Human primary epithelial cells from ADPKD cysts	[91,96,97,99–101,103]
Drug-induced nephrotoxicity	MDCK	[45,46]
	Mouse kidney tubule	[50,51]
	Human	
	Immortalized proximal tubule epithelial cells	[6]
	Primary proximal tubule epithelial cells	[34]
Fibrosis	Human proximal tubule epithelial cells with dermal fibroblasts	[48]
Renal cell carcinoma	Human RCC cells	[12,127–129]
Nephronophthisis	Mouse inner medullary collecting ducts cells	[130]