

Renal biology-driven macro and microscale design strategies for fiber-based technologies to create an artificial proximal tubule

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ABSTRACT

One in every six people in the world suffers from chronic renal disease. A cell-based Bioartificial Kidney (BAK) device is required due to the paucity of donor kidneys and the problems associated with Hemodialysis (HD). One of HD's flaws is that it lacks active solute transport, which is generally carried out by membrane transporters in kidney epithelial cells. Proximal tubule epithelial cells, in particular, play a key role in the active transfer of metabolic waste products. As a result, a BAK with an artificial PT capable of actively transporting solutes between the blood and the filtrate could offer significant

therapeutic benefits. A biocompatible tubular framework that supports the adhesion and function of PT-specific epithelial cells is required to create such an artificial PT. This scaffold should, in theory, structurally mimic the natural PT basement membrane, which is primarily made up of collagen fibers. Fiber-based technologies, like as electrospinning, are thus particularly promising for the production of PT scaffolds. The utilization of electrospinning technologies to create an artificial PT scaffold for *ex vivo/in vivo* cellularization is discussed in this paper. We compare the various electrospinning technologies currently available and specify the desired scaffold qualities for use as a PT scaffold. Potential technologies that may converge in the future, allowing for the effective and biomimetic incorporation of synthetic PTs in BAK devices and beyond, are also discussed.

Key Words: Scaffolds; Electrospinning; Proximal tubule; Basement membrane; Artificial kidney

INTRODUCTION

The homeostatic management of the water volume and solute content in the blood can be described as kidney function. This is accomplished through three processes carried out in the nephrons (filtration, secretion, and reabsorption) [1]. There are two types of solute transfer between the blood and the filtrate: passive and active. Membrane transporters in epithelial cells in the tubules of the nephron carry out the latter. These functions are interrupted in End-Stage Renal Disease (ESRD), and the kidneys are unable to maintain homeostatic solute levels and fluid volume, resulting in serious health problems. Recent technological breakthroughs may allow ESRD patients to reintegrate renal tubular functions without the need for a donor kidney.

Over half a million Europeans underwent renal replacement therapy for End-Stage Kidney Disease (ESKD) in 2016. While kidney transplantation is the ideal treatment, due to a shortage of donor kidney grafts, the majority of ESKD patients are treated with Hemodialysis (HD) or peritoneal dialysis [2]. Patients who receive HD have a 5-year survival rate of less than 50%, which is much lower than those who receive a kidney transplant (>90%). One reason contributing to the high mortality rate is HD's lack of excretion of big lipophilic and protein-bound solutes, which results in the accumulation of large protein-bound uremic toxins, which are linked to an elevated risk of cardiovascular disease.

A Bioartificial Kidney (BAK) device could be a possible answer to the present dialysis method's difficulties. Essentially, the BAK could improve on existing dialysis techniques by incorporating kidney tubule epithelial cells, which would allow active transport of solutes between the blood and the dialysate, facilitating the removal of uremic toxins bound to human serum albumin, such as indole sulphate and kynurenic acid [3]. Although growing transplantable kidney tissue in the lab would be ideal, the bioartificial technique appears to be a more feasible option that has previously been tested in clinical trials [4-5]. Given the kidney's complexity and various functional responsibilities, it's likely that a BAK device would include multiple synthetic functional units to solve the present treatment approaches' inadequacies. To adapt to specific cellular and/or metabolic needs, each functional unit may be created from a variety of production methods [6].

Humes, et al. demonstrated the benefits of employing renal tubular cells on polymeric scaffolds in combination with dialysis in patients with acute kidney damage over a decade ago. A Bio artificial Renal Epithelial Cell

System (BRECS) has been successfully included into a continuous flow peritoneal dialysis circuit in more recent iterations of this technology [7]. Adult human renal epithelial cells are cultivated *in vitro* on porous, niobium-coated carbon discs in the BRECS. The discs can then be clinically perfused with ultra-filtered blood or peritoneal fluid from extracorporeal HD or peritoneal dialysis circuits once the optimal cell density has been achieved. This method, when combined with the latter, could be developed into a portable BAK system that considerably enhances the patient's quality of life. Pre- and post-cell filters with a 65 kDa molecular weight cutoff achieve immunological separation and protection of the BRECS epithelial cells while also allowing tiny proteins and hormones to be secreted into the patient's blood circulation. The implantation of artificial renal tubules is another BAK technique for restoring renal tubular function in the patient. Although the research is still in its early stages, proof of concept tests have shown that Proximal Tubule Epithelial Cells (PTEC) may function *in vitro* for at least three weeks. Because the Proximal Tubule (PT) normally contributes to the release of big protein-bound uremic toxins that are poorly eliminated by HD, PTECs are particularly attractive for this research. Various studies have focused on determining the best scaffold characteristics for constructing a functional artificial PT. Incorporating PTECs into a BAK necessitates the creation of a supporting structure that allows cells to function normally. PTEC are linked to the Basement Membrane (BM) of the natural kidney. The PTEC form a monolayer that is required to achieve solute concentration differences between the filtrate and the blood. Nano sized fibres made of natural polymers like collagen make up the majority of the BM. These fibres are arranged in a fibrous network that is permeable to the PTECs' delivered solutes. Although it is possible to extract BM from human kidneys, this would result in a scarcity of the substance. The therapeutic potential of de-cellularized kidneys derived from animals has also been examined as an alternate method. De-cellularized extracellular matrix has been shown to support cells and influence cell destiny *in vitro*, but *in vivo* testing have had limited success due to immunological reactivity and thrombosis. Artificially manufactured fiber-based scaffolds are readily available and made of clinical-grade biodegradable materials, and they may be tailored to precise nano and macroscale features including fibre diameter, porosity, and scaffold thickness. Artificial scaffolds have already been tested to see if they can support a confluent PTEC monolayer in a functional state. Electrospinning is a versatile and low-cost approach for creating fibre scaffolds using a variety of natural and manufactured biodegradable materials at both the nano and microscale.

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Artificial biomimicry and natural proximal tubule basement membrane

Creating a replacement for the BM on which the PTECs are fixed is one of the challenges in constructing an artificial PT [8]. The PT BM is a fiber-based sheet like network that provides structural support to adherent cells and plays an important function in cell signaling and cell destiny while allowing solute and water exchange with the surrounding tissue. It is a component of the Extracellular Matrix (ECM). The epithelial cells deposit BM components while also releasing factors that destroy them, resulting in BM remodelling that is ongoing. Although there is little information on the tubular BM's turnover rate, it has been estimated to be in the multiple weeks range.

Renal scaffold design advancement using electrospinning strategies for vascular grafts

We reviewed the present applications of electrospinning technologies in the construction of PT scaffolds (to date, only solution electrospinning) and the encouraging outcomes. Other study fields that use electro spun scaffolds for (pre) clinical purposes, like as cardiovascular research, may bring fresh ideas and methods to improve PT scaffold design. Indeed, studies showing that electro spun scaffolds can build viable and functioning tissue engineered vascular systems *in vitro* and *in vivo* backs up the promising outcomes of several advanced electro spun designs.

Disease simulation

Several effective attempts to use kidney organoids as a novel disease-modeling platform have recently been reported in studies. Organoids produced from iPSCs or adult kidney tubular epithelium are genetically heterogeneous and match the complex *in vivo* environment better than lineage-restricted cell lines. The availability of numerous cell types allows researchers to analyse the disease microenvironment *in vitro*. Furthermore, the organoids' 3D cell cultures represent a key step in a trend toward more physiologically appropriate tissue models. In the case of glomeruli, 3D organoid-derived glomeruli had higher gene expression linked with slit diaphragm components, renal filtration cell differentiation, and glomerular growth than 2D cultures.

When designing a synthetic proximal tubule, there are a few things to keep in mind. There are certain claims that may be made about the optimum scaffold qualities of the inner layer based on the properties of natural BM and current understanding of the performance of renal epithelial cells on electrospun scaffolds [9]. Although the luminal side of the scaffold supporting the epithelial cells should ideally match natural BM, which consists primarily of natural fibres with a diameter of 7 nm, epithelial cell viability was allegedly unaffected by fibre diameter.

Converging technologies for fabrication of next-generation synthetic proximal tubules

Although the focus of this review is on the potential use of fiber-based technologies in the development of PT scaffolds, combining these manufacturing technologies with more cell-friendly fabrication methods, such as bio printing, will likely yield more robust results with longer clinical applications [10]. Because of the complexity and diversity of native tissue, technology will eventually converge in order to reproduce this heterogeneity *in vitro*. Some of the features of electrospinning and bio printing are shared by using NFES with living cells, albeit at the cost of mechanical strength and product size restrictions. Recent advances in combining bio printing and MEW for the creation of mechanically competent structures that enable cell growth and differentiation, on the other hand, show promise for applications in the medical field.

CONCLUSION

Due to the shortage of donor kidneys and the ineffectiveness of current dialysis procedures, cell-loaded functional kidney scaffolds are required. We've compiled a list of research that looked at several electro spun scaffolds seeded with kidney epithelial cells. We also explored how alternative electrospinning processes could be used to improve build designs and presented a vascularization strategy. Recent research has demonstrated the ability of electro spun scaffolds to support renal epithelial cells and their solute transport capability, although they have only used SES as

a construction method. While SES has proven to be very effective for producing thin fibers, other methods without solvents, such as MES, MEW, and NFES, may also be investigated because they provide greater spatial control during fiber deposition or the ability to spin living cells intrafiber. We developed a concept for an artificial PT tubule based on a bilayered scaffold design incorporating growth factors, which was inspired by vascular scaffold design methodologies. To best sustain a confluent PTEC monolayer, we believe that the inner layer should be thin and include very fine fibers. The hydrogel in the outer layer should be physically supported by a low fiber density network of thick fibres that is porous enough for capillary vessels to integrate into the scaffold and develop into close proximity to the PTECs. SES would be best for the inner layer, while MES or MEW would be best for the outside layer, based on the desired fiber structures. VEGF looks to be the most promising of several growth factors that could be favorable to cellular development within the scaffold. More research is needed in this area to determine the practicality and viability of these concepts, as well as to completely integrate electrospinning technology into renal regenerative techniques. Before the requisite functionality and complexity of the synthetic PTs are obtained for translation and deployment in clinical use, an intermediary phase that generates a humanized *in vitro* testing platform for basic research and drug testing could be envisioned. As a result, an electro spun synthetic PT would need to be built with 3D *in vitro* testing in mind, i.e. for bioreactor applications, and might be beneficial in preclinical drug testing, for example. Future BAK devices could include an electro spun synthetic PT to promote epithelial cell activity in a hypothetical second stage, addressing the existing absence of absorptive and secretory functionalities in therapy alternatives. Finally, the proposed PT scaffold design might be scaled down to generate functioning nephron units, allowing the incorporation of other renal cell types and structures to construct a tissue engineered kidney. The *in vitro* bioreactor stage is crucial for establishing convergence of the PT with other portions of the functional nephron unit (e.g., the glomerulus) and for evaluating size reduction boundaries in order to achieve this final goal.

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